Editorial

Present Status of Cardiology in Japan

IN the previous issue of this journal, I mentioned about the past progress made in the field of cardiology in Japan. In the present issue I wish to describe the present trends of Japanese cardiology. The Japanese Circulation Society has now approximately 3,000 members and an astonishingly great number of papers have appeared in the field of circulation in the past few years. At present, there are 143 medical departments and laboratories of university, 12 institutes and many clinics of various hospitals, contributing to the Japanese Circulation Society. The general meeting is held once annually, and regional meetings are held in 6 districts.

I am going to introduce some of the cardiologists in each district in geographical order. It is to my regret to be able to give only brief notations of their projects that have interested investigators during the past few years. First of all, I shall begin with the southern part of Japan, the Kyushu District. At Kurume Univ., N. Kimura has long been known for his extensive work about clinical and experimental study of coronary heart disease, and is a pioneer of VCG in Japan. At Kyushu Univ., K. Yamaoka and his coworkers have been interested in myocardial metabolism, and S. Katsuki has long been studying the cerebral circulation.

In the Chugoku District, J. Mise at Yamaguchi Medical College has concentrated on the study of pulmonary hypertension and pulmonary wedge pressure in various diseases. K. Nishimaru has spent all his life in studying angiology and circulation of lymphatic and blood systems, and is the vice president of the Japanese College of Angiology.

In the Kinki District, M. Maekawa at Kyoto Univ. who is the prominent student of late Prof. T. Mashimo, one of the pioneers in cardiovascular study in Japan, holds many important positions in the Japanese Circulation Society. He is the editor in chief of the Japanese Circulation Journal, the official journal of this Society. Maekawa has proposed " chain doublet theory " in ECG and is one of the leading electrocardiographers in Japan. I. Donomae at Osaka Univ. has done excellent work in the genesis of myocarditis with reference to the general infection. T. Yoshida at the same University has made contributions in the understanding of the renal tubular transport mechanism, and the recent attempt of studying the cardiac function by use of the ultrasonic Doppler method is noteworthy. In the surgical clinic of Prof. Takeda, the successor of the former Prof. Ozawa, they have been interested in the cardiac surgery, particularly that of the valvular disease of the heart, by the use of extracorporeal circulation. T. Hara and his associates have been studying the circulation

and myocardial metabolism in the state of anoxemia. T. Tomomatsu of Kobe Medical College has challenged the subject of venous return and the genesis of pulmonary edma.

In the Tokai District, M. Takayasu from Mie Prefectural Univ. has been concentrating his work in the electrophysiological aspect of atrial function. At Nagoya Univ., in Prof. Hibino's Clinic, they have been carrying on the work of the depolarization process of the myocardium by using the contiguous bipolar lead and multi-intramural lead. H. Toyoshima at the Research Institute of Environmental Medicine, has made many important works in the fields of ECG and VCG by his reconstructing method. Y. Hashimoto of Nagoya Univ. has performed many cases of cardiac surgery by the direct vision approach.

The Kanto District is the biggest of all 6 districts in Japan and has 17 medical schools and many cardiovascular investigators. Above all, the Tokyo Univ. is the largest and acts as the center of all phases of academic medicine in Japan. As has been mentioned in the previous issue, the followers of the late Prof. K. Kure, represented by S. Okinaka, K. Oshima, S. Saito, T. Shimamoto, T. Kobayashi, H. Ueda and others have endeavoured in establishing the cardiovascular studies in Japan. At Tokyo Univ., S. Okinaka has done many studies on the neurohumoral regulation of circulation. T. Kobayashi is known for his work on coronary circulation and myocardial metabolism, and is a pioneer in the use of cardiac catheterization technique in Japan. S. Tasaka and associates are studying electrolyte metabolism and renal function. H. Ueda and colleagues are studying the cardiac function with the use of ECG, PCG, isotope and other techniques, especially in regard to the regulation of circulation. S. Kimoto in the surgical department, is one of the leading surgeons in the field of congenital cardiac lesions and has contributed to the progress in the achievement of heart-lung machine, brain cooling and artificial organs. K. Shimizu and his associates have done some interesting work on peripheral circulation by plethysmograhy. K. Matsuda in the physiology department has measured the myocardial membrane potential and pacemaker potential in dogs. At Chiba Univ., S. Saito introduced Wetzler-Böger's method for hemodynamic study in Japan and has endeavoured to use this method for the pulmonary circulation. At Nippon Univ., K. Oshima is one of the pioneers for the use of renal clearance test in Japan, and has been studying lipoproteins of Japanese by the ultracentrifugation method. Recently he also has organized the new Society for Renal Disease. T. Shimamoto at the Medical and Dental College in Tokyo has done work on arteriosclerosis and has proposed the hypothesis that substances capable of eliciting host response is the factor of producing atherosclerosis. Credit should be given to E. Kimura of Nippon Medical College for his contributions in the field of ECG such as studies of atrial fibrillation, coronary branch insufficiency and other experimental investigations. At Keio Univ., I. Mikata has continuously studied the experimentally produced bacterial endocarditis. Also at the

Keio Univ., T. Aizawa has carried out many clinical evaluations of cerebral circulation especially in cerebral vascular accidents. K. Yamakawa of Juntendo Univ. is known as the original investigator of intracardiac phonocardiography. At Tokyo Women's Medical College, S. Sakakibara is one of the most prominent cardiac surgeons in Japan, and has collected more than 2,000 cases of mitral valvular disease. M. Murakami at Kanazawa Univ. has attacked the problem of arteriosclerosis in respect to the fat metabolism and blood coagulation.

In the Tohoku District, there are only few cardiologists. K. Nakamura of Tohoku Univ. has been studying the pathophysiology of bronchial circulation. At the Torikai's clinic at the same Univ., they have been working on body fluids by isotope technique.

In the past decade or so, the importance of cardiovascular disease has been emphasized in Japan. In 1955 " The Heart and Blood Pressure Institute " was established in Tokyo Women's Medical College. S. Sakakibara has been in charge of the institution. Affiliated with Kurume Univ. in Kyushu District, " Institute of Cardiovascular Disease " was established last year. The director of the institute is N. Kimura. At Kyushu Univ., the Cardiovascular Institute was founded a few years ago. K. Yamaoka is in charge of the institute. The recently established " Center for Adult Diseases, Osaka " (director: A. Imamura) concerns primarily with the diagnosis and prevention of cardiovascular disease. These institutes are all governmental or belonging to the university. In Tokyo, on the other hand, a private institute " The Cardiovascular Institute " is going to be established and S. Koyama from Tokyo Univ. is to be the director of the institute.

Japan has some periodicals publishing papers in the cardiovascular field. Two of the eminent journals are Japanese Circulation Journal, official journal of the Japanese Circulation Society, and Respiration & Circulation. Some of the papers in the field of circulation have appeared in the official journals of the Japanese Society of Internal Medicine, Surgery, Physiology and others. The majority of them are, however, written in Japanese and some have only English resumes and abstracts. There are many English editions of journals in the field of general medicine, that is, Japanese Journal of Physiology, Japanese Journal of Pharmacology, Japanese Journal of Experimental Medicine, Japanese Journal of Medical Science & Biology and others. Besides these, Kyoto, Tohoku and some of the other universities have their own bulletin written in English. In spite of these, in the field of circulation, English editioned Respiration & Circulation and Bulletin of Heart Institute published by the Heart and Blood Pressure Institute, are the only journals editioned completely in English, both being annually published.

Although a number of journals or bulletins have been published, there still are not enough English editioned periodicals concerning cardiovascular disorder. We felt that it is very important to publish a journal in English in order to introduce many works and studies carried out in Japan

in the field of cardiovascular disease, and this is the reason why we have published this Japanese Heart Journal.

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Balneotherapy for Hypertension

with Special Reference to the Factor Analysis of the Effects of Spa Treatment on Hypertensive Patients

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A therapeutic effect of balneotherapy on hypertension has been proved in Kageyu Hot Springs (simple thermals). It was effective not only in lowering high blood pressure, but also in amending ECG abnormalities, increasing renal blood flow and glomerular filtration rate. These effects continue without additional therapy even 3–6 months after the treatment. An experimentally established fact suggests that it will also have an antilipemic or antiatherosclerotic activity on the hypertensive patients. However the real indication of balneotherapy for hypertensive patients will be given in the cases where the degree of arteriolosclerosis is limited, for the patients with albuminuria or abnormal ECG showed lesser decrease in blood pressure than the patients without such complications and advanced atherosclerosis in the animals induced by cholesterol feeding could not be improved by a series of balneotherapy for only 3–6 weeks.

In addition to these findings, the authors applied factor analysis to the several physical measures in the living body and observed how the structure pattern of the circulatory function varied through the spa treatment. As a result, the pattern changed on the 10th day abruptly and approached the normal pattern obtained from the factor analysis on healthy people in the previous studies.

SEVERAL spas have been known in Japan since prehistoric days for their beneficial effect on hemiplegics like " Chubu no yu " (Hot spring for postapoplectic disorders). However thorough scientific study of these spas was first undertaken on the nation-wide basis when the subject of " spa treatment of hypertension " was given a Grant in Aid for the Scientific Research of the Ministry of Education in 1956 and it continued from that time on for

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next 3 years. As a result of these investigations, it was demonstrated that the serial bathings in sulfur springs, radioactive springs, carbonated earthy springs, and weakly muriated springs, and simple thermals produced a hypotensive effect on the patients with hypertension.

This paper deals mainly with the studies carried out in the Kageyu Spa (simple thermals). It is to be noted specially at this point, that the present authors applied the method of factor analysis[1)-4)] for the first time in this research field in order to get an integrated view with respect to the effect of hot spring treatment on the circulatory disturbance, and would like to take this occasion to emphasize that this analytic method would work very well in studying these multi-facet phenomena.

Materials and Results

The subjects in these studies include 244 hypertensive patients with systolic

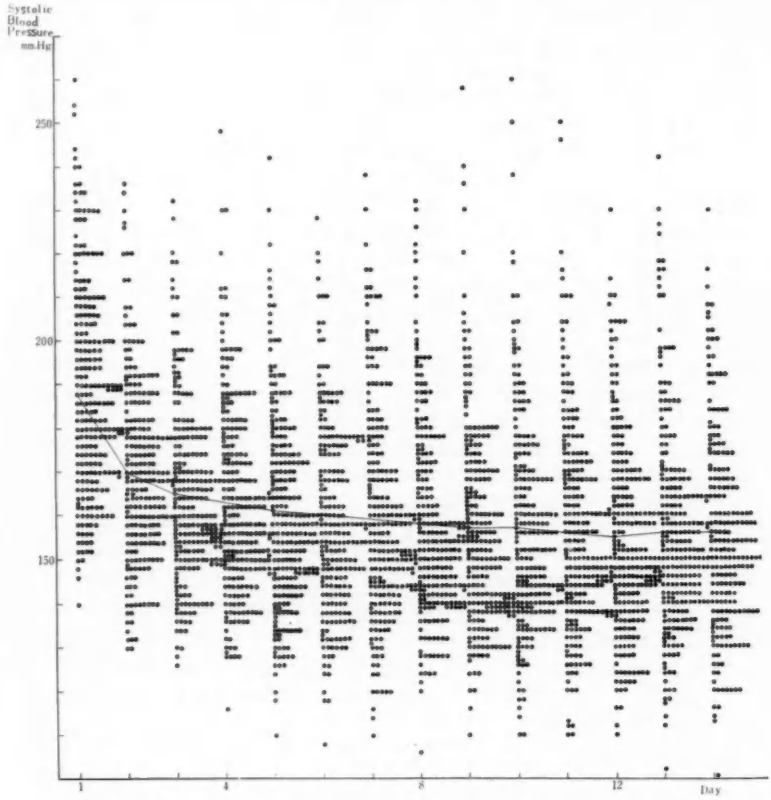

Fig. 1, a. Changes in systolic blood pressure during the spa-treatment.

blood pressure of over 150 mm.Hg and/or diastolic blood pressure of over 90 mm.Hg.

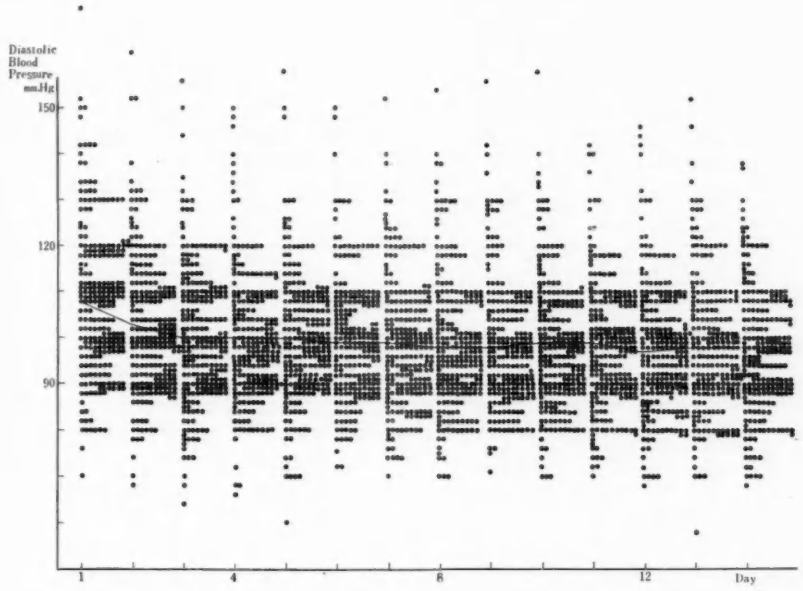

Fig. 1, b. Changes in diastolic blood pressure during the spa-treatment.

As the Fig. 1 shows, a hypotensive effect was particularly apparent during the first week of serial bathings, and the most significant fall of blood pressure which appeared on an average on the 12th day of the treatment was maintained throughout the whole course of the successive days of bathing within a small range of variation.[5] These changes in the blood pressure were obviously statistically significant. The lowering of systolic blood pressure over 20 mm.Hg was observed in 68.6% of the 223 cases with the initial systolic pressure over 150 mm.Hg. As this tendency of the blood pressure changes during the serial bathings was also confirmed with a reasonable statistical significance by a single thermal bathing, the hypotensive effect of spa-treatment on a patient could be foreseen by checking the effect of a single bathing. Furthermore, the state of lowered blood pressure brought about as a result of spa-treatment was observed in 70% of the cases and was maintained even after 3 months as confirmed by the follow-up studies.[6),7)]

Discussion of the curative effect of balneotherapy on the hypertensive disease should not be limited to the changes in blood pressure at the brachial artery alone, but it must be extended to the changes of generalized circulatory disturbance as a whole. In this connection the authors measured the arterial pressure in the ocular fundus in 28 patients and found that it fell through the

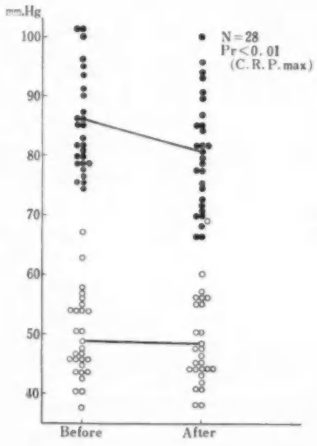

Fig. 2. Changes in retinal artery pressure by the serial bathings.

spa-treatment by 4.8 mm.Hg on an average, and that this fall in retinal artery pressure correlated with the disappearance of subjective symptoms of the patients such as headache, dizziness and tinnitus. But in the patients whose ocular fundus showed severe arteriolar sclerosis, the lowering of blood pressure was hardly observed.

The rise in blood pressure and/or decrease in amplitude of plethysmography as a reaction to the application of cold were specially marked on the 7th day of the treatment and returned to the initial level again after 2 weeks. When these cold reactions deviated from the normal range, either too high or too low, at the onset of the treatment the changes for a hypotensive effect of spa-treatment became poorer. The previous reports indicated that the ECG findings during the spa-treatment did not change significantly after a single bathing,[8),9)] while the serial bathings showed an improvement of ST-T or T changes in the cases with myocardial lesion, when the fall of blood pressure was very slight; but the cases with myocardial damage accompanied by a marked fall in the blood pressure showed an aggravation of ECG findings during the spa-treatment. In total our data in the Kageyu Spa revealed, that of the 54 patients with myocardial lesion, 32 cases (59.3%) were improved, 12 cases did not show any change and 10 cases (18.5%) showed aggravation of ECG findings. The improved state was maintained after 6–8 months in 8 out of 12 observed cases and in 4 cases (33.3%) it returned to the pre-treated level in follow up study. The hypotensive effect was less remarkable in the cases with severe ECG abnormalities than that in those with no or slight ST-T changes. This difference was statistically significant at a 1% level.

Inconstant changes of renal function in older people by the hot spring treatment had been reported by Tasaka *et al.*[10)] Similar finding was obtained in the Kageyu Spa after a single bathing, while through the serial bathings the glomerular filtration rate (GFR) and renal plasma flow (RPF) were

Table I. The Influence of Myocardical Lesions on the Hypotensive Effect of the Spa Treatment

Decrease in systolic blood pressure → / ↓ Myocardial lesion	>20mm. Hg	<20 mm. Hg	Total
−	63 (75.0%)	21 (25.0%)	84
+	27 (46.6%)	31 (53.4%)	58
Total	90	52	142

$\chi^2 = 12.04$ $P_r < 0.001$

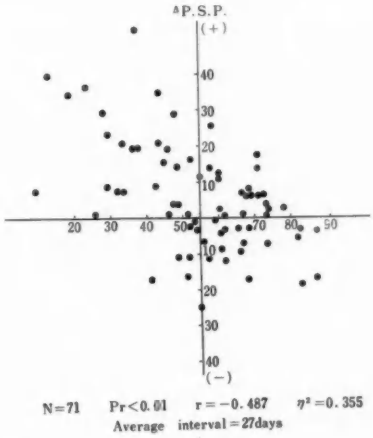

Fig. 3. Changes in the value of PSP test by the serial bathings.

increased on average by 9.2% and 12.9% respectively.[11] These increases were observed in practically all the patients with GFR and RPF under 100 ml./min. and 500 ml./min. respectively. These findings were supported by PSP test in

Table II. The Correlation of the Blood Pressure Changes and the Values of PSP Test

Decrease in systolic blood pressure → / ↓ 15 minute value of PSP test	>20 mm. Hg	<20 mm. Hg	Total
25%<	28 (68.3%)	13 (31.7%)	41 (100%)
〃 >	41 (77.4%)	12 (22.6%)	53 (100%)
15%<	46 (71.9%)	18 (28.1%)	64 (100%)
〃 >	23 (76.7%)	7 (23.3%)	30 (100%)
10%<	58 (74.5%)	20 (25.5%)	78 (100%)
〃 >	11 (68.8%)	5 (31.2%)	16 (100%)
Total	69 (73.4%)	25 (26.6%)	94 (100%)

71 patients, which was carried out before the treatment and on the 27th day of the serial bathings. The hypotensive effect was significantly different between the patients with proteinuria and those without it, but was not to be foreseen by the variation of PSP test.

Discussion

From the above mentioned observation in Kageyu, the conclusion may be drawn that the spa-treatment for hypertension is reasonably indicated for those suffering from angiospastic hypertension, while it is not necessarily effective, when arteriosclerosis is advanced beyond a certain critical level (say, III Grade in the Scheie's classification of arteriolosclerosis in the ocular fundus or severe myocardial lesion). The renal function and ECG findings would also be improved in those cases where reverible change is a predominant factor of hypertension.

Interestingly enough, the improvement in various aspects of these hypertensive patients could last many months after the discontinuation of the treatment, and there should be some explanation for this prolonged effect of spa-treatment. The presence of the vicious cycle in cases of hypertension which proceeds in the following order (rise in blood pressure—angiospasm—arteriolosclerosis—decrease in renal blood flow—and exaggerate blood pressure), may be broken, though not completely, by the spa-treatment. Experimentally, thermal bathings in Kageyu inhibits hypercholesteremia and development of atherosclerosis in cholesterol-fed rabbits[12] which may further support the above mentioned hypothesis though their antilipemic or antiatherosclerotic activity will require further elucidation.

As it is well known that hypertensive patients are not suffering merely from the high levels of systolic blood pressure in the brachial artery alone, but hypertension must be looked upon as a kind of generalized circulatory disturbance as a whole. This may be tentatively called as a state of "imbalanced functions (especially the imbalanced circulatory function) of the living body." From this point of view some method of whole study of many functions measured on the subjects is necessary in order to get an adequately integrated criterion on the effectiveness of the hot spring treatment of hypertension. Factor analysis would seemingly suffice such requirements, as the analysis has been found and developed by the hands of psychologists for the purpose of classifying innumerable psychological or intelligence tests to obtain various patterns in the personality of human being. They succeeded in this way in reducing the number of the tests necessary to describe these psychological patterns of individuals.

The mathematical procedure of factor analysis consists in classifying the calculated correlation coefficients between any 2 of the measured tests by their respective distance. By doing so several independent axes are obtained which can correspond to certain major trends in individual personalities.

Very analogically, this method may be used in explaining medical

phenomena, and the multiple functions of the living body will by this means form bunches of several independent systems each of which will represent in a sense an actual regulating system in the body. In this way, if measurements on the multiple functions of the hypertensive patients are followed up during a series of bathings in the hot springs, it will be known how the imbalanced patterns of the circulatory systems will be normalized. The observation of this was made on a group of 100 healthy people and was reported at the 32nd Conference of the International Statistical Institute by one of the authors, K. Takahashi.[13]

The calculation was made on the means and variances of the measured systolic blood pressure, diastolic blood pressure, pulse pressure, pulse rate and body temperature and on the correlation coefficients between any 2 of them, on the 1st, 2nd, 3rd, 7th, 10th, 12th-14th day of the spa-treatment with respect to 78 hypertensive patients who came to Kageyu Spa from September, 1956 to November, 1959.

The process of change in the mean values is shown in the Fig. 4; all the measured values decreased abruptly between the first and second day

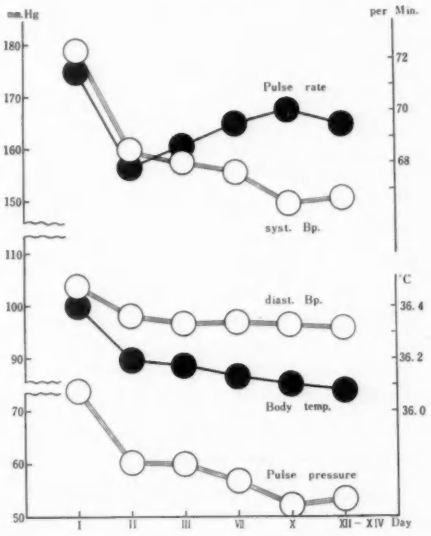

Fig. 4. Changes in the mean values.

and most of them still kept decreasing thereafter, except that the means of pulse rate had a tendency to increase from the second day. The body temperature and diastolic blood pressure were gradually decreasing until the last day of the observation while the systolic blood pressure and pulse pressure began to rise again from the 10th day, when they marked their lowest values. The component analysis of the correlation matrix between the above mentioned 5 tests (where the solution of component axes is given, so as to minimize the

Table III. Correlation Matrix

	T. 1 Body temp.	T. 2 Pulse interval	T. 3 Max. BP	T. 4 Min. BP	T. 5 Pulse pressure
T. 1 Body temp.					
	—.2157				
	—.1357				
T. 2 Pulse interval	—.3260				
	.0795				
	.0698				
	—.0437				
	.0565	.1196			
	—.0136	.0346			
T. 3 Max. BP	—.0480	—.1955			
	.0320	—.0519			
	.0669	—.0969			
	.0129	—.0857			
	.0586	—.0262	.6437		
	.0625	—.1807	.6689		
T. 4 Min. BP	—.1678	—.3574	.5811		
	—.0567	—.2627	.5644		
	.0566	.0025	.6698		
	—.0054	.0963	.7815		
	.0360	.1789	.8648	.0596	
	—.0504	—.0983	.7498	.1754	
T. 5 Pulse pressure	.1598	—.0174	.8328	—.1841	
	.1160	.1418	.7671	—.0909	
	.0305	—.1528	.7276	.0332	
	—.0446	—.1551	.3834	.0620	

Correlation coefficients corresponding to 1st, 2nd, 3rd, 7th, 10th and 14th day are indicated.

Table IV. Proper Values

	α	1st	2nd	3rd	7th	10th	14th
	1	2.14	2.10	2.02	1.92	2.11	1.90
	2	1.25	1.24	1.36	1.39	1.11	1.17
λ	3	0.93	0.90	1.27	0.95	0.97	0.98
	4	0.73	0.70	0.45	0.74	0.85	0.80
	5						
	1	42.8	42.0	40.4	38.4	42.2	38.0
$\sum\lambda/p$ (%)	2	67.8	66.8	67.6	66.2	64.6	61.4
	3	86.4	84.8	93.0	85.2	81.4	80.1
	4	101.0	98.8	102.0	100.0	98.4	97.0

Table V. Proper Vectors

(Multiplied by $\sqrt{\lambda}$)

Component		f. 1	f. 2	f. 3
$\sqrt{\lambda}$		1.56	1.20	0.99
1st day	T_1	.082	—.7744	.4927
	T_2	.2101	.8168	.0361
	T_3	1.0065	—.0558	—.0166
	T_4	.6125	—.3644	—.7049
	T_5	.8334	.1927	.4888
$\sqrt{\lambda}$		1.50	1.11	0.95
2nd day	T_1	—.0048	—.6131	.7515
	T_2	—.0185	.7782	.4240
	T_3	1.0133	.0471	.0248
	T_4	.7511	—.3874	—.2351
	T_5	.8118	.3136	.2010
$\sqrt{\lambda}$		1.42	1.17	1.13
3rd day	T_1	—.1129	.2404	—.8819
	T_2	.4326	.4611	.6373
	T_3	—.9867	.0970	.2395
	T_4	—.5618	—.7722	.1821
	T_5	—.7263	.7025	.0505
$\sqrt{\lambda}$		1.39	1.18	0.98
7th day	T_1	.0912	.3966	.9193
	T_2	—.0878	.7185	—.2480
	T_3	1.0002	—.0060	—.0638
	T_4	.5570	—.6688	.1524
	T_5	.7781	.5211	—.1628
$\sqrt{\lambda}$		1.45	1.05	0.99
10th day	T_1	—.0869	.5169	.8054
	T_2	.1960	.7173	—.1393
	T_3	—1.0046	.0571	—.0502
	T_4	—.6596	.4541	—.4535
	T_5	—.2826	—.3337	.3224
$\sqrt{\lambda}$		1.38	1.08	0.99
14th day	T_1	.0196	.3305	.9417
	T_2	.0840	.7739	—.2361
	T_3	—.9610	.0337	.0260
	T_4	—.8595	.3659	—.1167
	T_5	—.4844	—.5685	.1524

sum of squares of the observed values projected onto the axes) revealed that the test space was composed of 4 components, the 4th component of which could be discarded with commiting errors of only 5–20% (Table III to V). Thus a state of " functional balance " is considered, defined in a group of

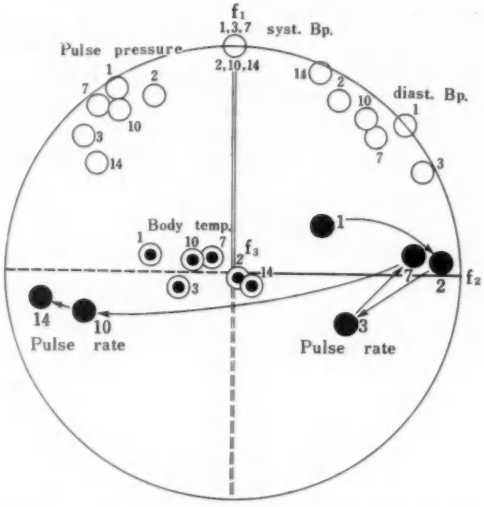

Fig. 5, a. The end points of the test vectors projected onto the f_1 and f_2 subspace.

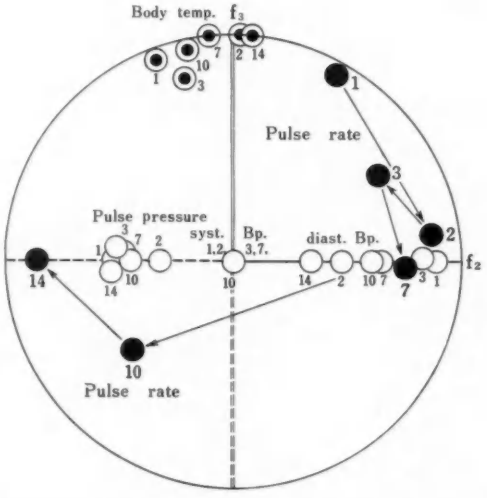

Fig. 5, b. The end points of the test vectors projected onto the f_2 and f_3 subspace.

individuals in the 3 dimensional space of the tests in which the systolic blood pressure, pulse rate, body temperature made up 3 independent components. As is shown in the Fig. 5, the vectors corresponding to the tests are indicated by unit vectors in the directions of the respective axes. It may be called the " plane of circulatory system " which is spanned by the systolic blood pressure and pulse rate, and the diastolic blood pressure and pulse pressure are included on that plane being correlated with the pulse rate in opposite ways (Fig. 5, a and b).

This structure pattern of test vector space remained almost constant until the 7th day of the spa-treatment, inspite of marked changes in each mean value of the test variables (Fig. 6). In other words, the higher the di-

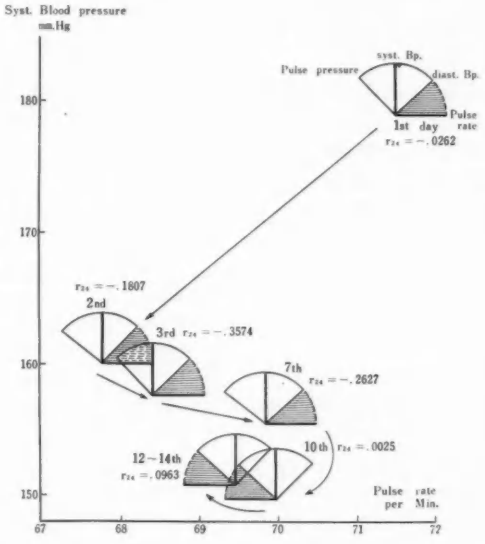

Fig. 6. Movements of the center (means) and pattern change (situation of test vectors).

astolic pressure, the faster the pulse rate. After 10 days, on the other hand, where most of the functions may be assessed as soothed, the pulse rate vector came into an opposite direction on the " circulatory plane ", which means the lower the diastolic pressure, the faster the pulse rate. It follows from this interesting result that the change of the mean values is one thing and the pattern change is another.

If the after-10-day patterns are more akin to that of the normal group (which might be inferred from our previous reports on the factor analysis of 7 kinds of tests on 100 healthy female students[14]), it might be said that the abnormally distorted pattern in the vectors of the circulatory plane was nor-

malized by the spa-treatment. This apparent normalization of the pattern does not promise at once, that it means a favorable effect on hypertensive patients, because the pattern itself was defined in a group, not in each individual person. Nevertheless it is an interesting finding, as it might profit us in giving a criterion of certain therapeutic agents on human being as such.

The factor analysis of 40 kinds of functions measured on 100 healthy female students,[12] as was mentioned previously, resulted in having roughly 3 major groups, namely adrenocortical, adrenomedullary, and thyroid systems. The diastolic blood pressure was then situated in a complicated relation to the chemical constituents of body fluids governed by the adrenal cortex and the systolic blood pressure was influenced rather by the adrenomedullary function. These facts suggest the importance of paying attention to the variation of the chemical constituents in the blood in the study of spa-treatment of hypertension.

The 12th day of the spa-treatment which was originally rated as the last day of change in the blood pressure seems to be the beginning day of the pattern change. Adding more variables (especially chemical constituents in the blood and urine) to the factor analysis, the authors intend to clarify the meaning of the critical 12th day again in near future.

Summary

(1) The bathing cure in the Spa Kageyu produced a long-term hypotensive effect on the patients with hypertension.

(2) The beneficial effects of the spa-treatment on hypertensive patients were not limited to the hypotensive effect alone but extended to the improvement in the ECG and renal functions and to the fall in arterial pressure of ocular fundus and in body temperature.

(3) The factor analysis with respect to the measured systolic and diastolic blood pressures, pulse pressure, pulse rate, and body temperature showed 3 independent axes, 2 of which composed a circulatory plane. The patterns of the test vectors on a circulatory system were constant until the 10th day, then changed abruptly to an opposite pattern concerning pulse rate and diastolic blood pressure on the 12–14th day.

In view of the fact that diastolic blood pressure was correlated with chemical constituents of the body fluids, further studies in this field will be carried out to elucidate the mechanism of the abrupt change in the circulatory pattern.

Appendix

Mathematical calculation of factor analysis may be performed in the following oder.

1. Observation of p kinds of tests on n individuals.

$$\begin{vmatrix} X_{11} & X_{12} & \cdot & \cdot & \cdot & X_{1n} \\ X_{21} & X_{22} & \cdot & \cdot & \cdot & X_{2n} \\ X_{31} & X_{32} & \cdot & \cdot & \cdot & X_{3n} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ X_{p1} & X_{p2} & \cdot & \cdot & \cdot & X_{pn} \end{vmatrix}$$

where in X_{ij} i the number of test
j the number of person

2. Calculation of correlation matrix.

$$\begin{vmatrix} 1 & r_{12} & \cdot & \cdot & \cdot & r_{1p} \\ r_{21} & 1 & \cdot & \cdot & \cdot & r_{2p} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ r_{p1} & r_{p2} & \cdot & \cdot & \cdot & 1 \end{vmatrix}$$

where r_{jk} indicates the correlation coefficient of the two tests, j and k with respect to n individuals

3. Structural model of observed values will be given in the formula:

$$X_{ij}=(a_{j1}f_{1j}+a_{j2}f_{2i}+ \cdots +a_{jm}f_{mi})+b_jS_j$$

a: common factor loadings
b: specific factor loadings
$m = 1, 2, \ldots, \alpha, \ldots, m \leqq p$

Factor loadings $a_{j\alpha}$ correspond to the correlation coefficient between the test X_j and the factor f_α.

4. Theoretical structure of correlation coefficients is thus given in the formula:

$$r_{jk} = a_{1j}a_{1k}+a_{2j}a_{2k}+ \cdots +a_{jm}f_{km}+b_jb_k$$

In factor analysis only the common factors are taken into consideration.

5. Calculation of factor loadings is carried out in the following two different methods.

In factor analysis: Centroid method
In component analysis: Solution of the characteristic equation.

6. Geometrical representation.

p test vectors τ_j ($j = 1, \ldots$ p), which are projected into the m dimensional test space, are constructed by m factor loadings.

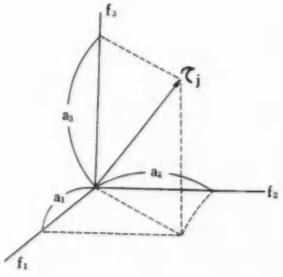

Fig. 7. Geometrical representation.

The test vectors bunched in a cluster in this space are constructed from the same factors, and the clusters orthogonal to each other are independent to each other.

Thus the factor analysis is applicable to classify the tests from the view point of the structural pattern of the factors.

7. Estimation of the individual score corresponding to each factor.

See the literatures.[1)-4)]

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Open Heart Surgery under Hypothermia

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Fourty-three operations were performed on a total of 41 patients consisting of atrial septal defect, ventricular septal defect, ventricular septal defect with pulmonary stenosis, tetralogy of Fallot, aortic valve stenosis, pulmonary valve stenosis and coarctation of the aorta under hypothermia using intrathoracic rewarming. All patients but 2 cases with tetralogy Fallot have been completely cured. From these experiences the safe time limit for cardiac occlusion is believed to be about 15 minutes, and operation such as ventricular septal defect with pulmonary stenosis can be performed under hypothermia.

STUDIES of hypothermia in the application purpose for open heart surgery were first made by Bigelow[1),2)] in 1950. Lewis and Taufic[3)] applied these studies to the operation of atrial septal defect in 1952 and published the report in January, 1953. From this time on, the clinical experiences were reported by Cookson,[4)] Neptune and Bailey[5)] (1952) and Swan *et al.*[6),7)] (1953).

Besides hypothermia to occlude the cardiac circulation in open heart surgery extracorporeal circulation has been employed in recent years. Both must be used according to their particular specifications. Hypothermia can be used more simply than extracorporeal circulation. On the other hand, for the extracorporeal circulation, a complicated artificial heart-lung apparatus must be employed, and also a large quantity of blood to fill the apparatus and many skilled operators are necessary. Even if its large expense could be discounted, extracoporeal circulation can not be performed outside of an extremely well-equipped hospital. Moreover, by this system the blood must be led to outside of the patient body and pass through the complicated apparatus, therefore, even if the apparatus has been greatly improved, there is a great possibility of damaging and the side effects such as hemolysis or other blood injuries. With regard to this we may conclude that hypothermia is less harmful and more physiologically effective than extracorporeal circulation. On the other hand, under hypothermia, when the heart is cooled, the sensibility of the heart muscle increases and then ventricular fibrillation is most apt to occur.[8)] Ventricular fibrillation can be easily prevented and

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when it does occur can be easily checked and not is fatal. However much the technique of hypothermia can be improved, there will always be a limit to the cardiac occlusion time. Thus we conclude that due to continual improvement of both operator and machine it will be possible to occlude cardiac circulation for a longer period of time.

The permitted occlusion time of hypothermia is prolonged due to the decrease of the body temperature and not due to the artificial substitution of any function. Even if an accident would occur during cardiac occlusion, we could take measures to check it within the limit of occlusion time. Of course we know it is very serious to interfere with the brain circulation even for several minutes under normothermia. The combination of extracorporeal circulation and hypothermia has been studied in order to decrease the flow of extracorporeal circulation.[9] Hypothermia should be considered as a safety valve in case of an accident.

In view of this we think that the less harmful hypothermia should be employed for the operation which can be performed within a limited occlusion time and extracorporeal circulation for the complicated operation which requires a longer period.

We believe that, under hypothermia, it would be physiologically sound to keep the temperature of the thoracic region higher than that of the body surface, consequently exerting a favorable influence on the general circulatory condition.[10),11] When the heart is cooled, the contraction power of the heart muscle is weakened and accordingly the cardiac output decreases. If the temperature of the thoracic cavity is much lower than that of the body surface, it may be difficult to maintain the proper amount of circulating blood to provide necessary oxygen for the metabolism in the peripheral tissue of higher temperature. This fact presents a problem at the time of rewarming.

With these considerations in mind, it would be reasonable to cool from the body surface and rewarm from the thoracic cavity. For the intrathoracic rewarming, we pour physiological saline solution of 40°C into the throracic cavity, and aspirate cooled solution through the tube inserted in the bottom of the thoracic cavity. When the rectal temperature rises to 32 to 33°C, we begin to rewarm with blanket in stead of intrathoracic rewarming and then close the chest.

The contraction of the heart muscle becomes stronger when the heart is rewarmed, maintaining high arterial pressure in contrast with a lower body temperature.[12] On the other hand, the body temperature rises rapidly because of the rewarming through out the lungs. Considering the surface rewarming, the rate of rewarming must be controlled, but there is no trouble encountered in the intrathoracic rewarming even though it is done rapidly, as peripheralization does not occur.

Animal Experiments—

In the animal experiments, oxygen saturation of the blood of venae cavae

decreases during cooling and immersion rewarming, naturally increasing the arteriovenous oxygen difference. On the contrary, venous blood oxygen saturation rises during the intrathoracic rewarming, therefore the arteriovenous oxygen difference decreases (Fig. 1 and 2).[13] Considering this fact there is a reason to believe that during the intrathoracic rewarming, the heart does maintain the proper amount of circulatory blood to provide necessary oxygen for the metabolism in the peripheral tissue, but that during the immersion rewarming it does not.

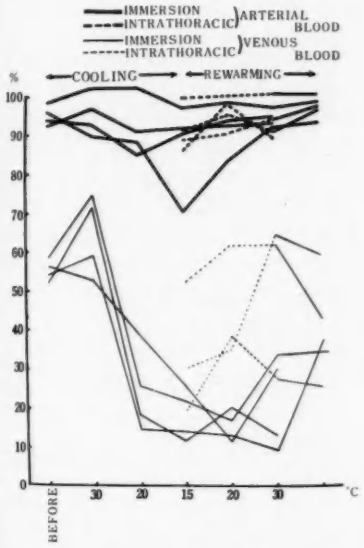


Fig. 1. Oxygen saturation of the blood.

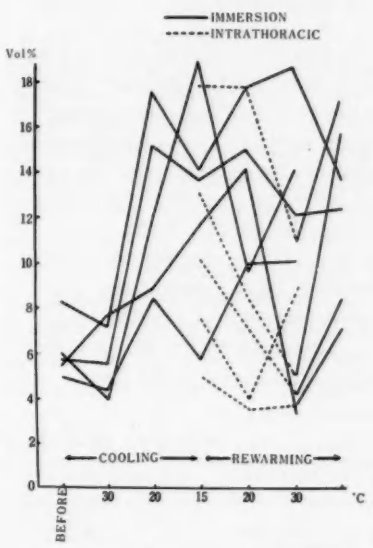


Fig. 2. Arteriovenous oxygen difference.

Under hypothermic condition, ventricular fibrillation occurs at a higher rate among patients with myocardial damage, and these patients have been considered to be contraindication for the use of hypothermia. Doubting this, we performed the following animal experiments. Myocardial damage was induced in dogs by ligating the anterior descending branch of left coronary artery. When ECG revealed myocardial damage about 2 weeks after the ligation, we opened the right ventricle under hypothermia, then assisted the animal's recovery by intrathoracic rewarming. Regarding survival rate of the experimental animals, only 27.7% survived in the immersion rewarming, but 75% in the intrathoracic rewarming. However, when intrathoracic rewarming was applied to the dogs with experimental myocardium damage, we found a 70% survival rate (Table I). This fact indicates that hypothermia can safely be applied to the subject with damaged myocardium when intrathoracic rewarming was employed. Even when ventricular fibrillation occurs,

Table I. Relation of Rewarming Method and Survival Rate

		Experiment	Survival	Survival rate
Immersion rawarming	Healthy	18	5	27.7%
Intrathoracic rewarming	Healthy	32	24	75.0%
	Damaged * myocardium	10	7	70.0%

* Dogs with experimentally ligated anterior descending branch of the left coronary artery.

if the heart is warmed, contraction power of the myocardium becomes stronger. Then the arterial pressure, consequently affecting coronary circulation, can be easily maintained by massage, so defibrillation by an electric shock becomes highly effective. By intrathoracic rewarming we are able to raise the body temperature quickly after the release of the cardiac occlusion, thus increasing the body temperature beyond optimal limit to ventricular fibrillation before closing the chest. Furthermore, it also increases the possibility of measuring the arterial pressure by auscultation. This helps also to prevent postoperative bleeding. Considering the above reasons we believe that the intrathoracic rewarming should greatly contribute to cardiac surgery.

The most important complication is considered to be ventricular fibrillation. As the Table II shows abnormal cardiac rhythms observed by our

Table II. The Effect of Anesthetics on the ECG

		30~25°C	25~20°C	below 20°C
Nembutal 8 cases	Ventricular rhythm	0	0	4
	A-V block	0	0	0
	Ventricular fibrillation	0	0	3
Thiopental 18 ceses	Ventricular rhythm	0	1	8
	A-V block	0	0	0
	Ventricular rhythm	0	2	1
Ether 22 cases	Ventricular rhythm	0	0	1
	A-V block	0	0	2
	Ventricular fibrillation	0	1	0

animal experiments were extrasystole, ventricular rhythm, A-V block, ventricular fibrillation and so on. These abnormal rhythms were frequently observed in cases less than 25°C in body temperature and were also influenced by certain anesthetic drugs. Abnormality appeared most frequently when

Nembutal was used; the least when ether was used.[14), 15)] Many preventive methods against ventricular fibrillation have been studied and published. We have selected from these methods hyperventilation to maintain pH, and prostigmine injection and sometimes coronary perfusion when occlusion time was necessary to be extended.

When the body temperature has dropped by about 60 per cent of the desired value, cooling is stopped and immediately after this 0.25 to 0.5 mg. of prostigmine is injected intravenously. The same dosage used intravenously is again injected immediately after cardiac occlusion into the coronary artery via the aorta. Ventricular fibrillation was prevented in almost all cases by prostigmine and even when it did occur, easily checked by electric shock.

The pulse rate already slowed by hypothermia becomes steadily even slower by prostigmine injection to the coronary artery, making the operative procedures easier. However, as the cardiac pulsation does not stop in the operation of atrial septal defect, it is easy to recognize coronary sinus from which venous blood flows out in accompaniment with pulsation. In the operation of ventricular septal defect we can also easily find the defect from which arterial blood flows out with pulsation.

At first, the operation of atrial septal defect was performed by thoracotomy on the 5th intercostal spaces of both sides according to Derra's technique. But it was easier to fix the sternum when the thoracic cavities were opened on the 4th intercostal space. Moreover, we believed that the one side thoracotomy would have less influence on the postoperative respiratory function than the both sides thoracotomy. Because it was difficult to perform one operation by opening the right thoracic cavity from a left side position, we finally decided to operate on the right thoracotomy by cutting the sternum. But even then both thoracic cavities were sometimes unintentionally exposed.

The circulations of venae cavae were occluded by looping securely and that of the aorta and pulmonary artery by clamping with forceps through sinus transversus pericardii. If the heart pulsates several times after occlusion of inflow, it shrinks the heart, since the blood flows out from the heart and lungs. We occluded the outflow at that time and reduced the bleeding from the atrium at the incision. However, when the blood volume in lungs markedly increases by pulmonary engorgement, in spite of this procedure, much of blood volume will be lost at the atrial incision.

In order to remove air from the atrium when closing the defect or incised wound, at first we poured a physiological saline solution into the atrium, but lately for this purpose the occlusion of inferior vena cava was properly released filling the atrium with blood. Attempts were made using this procedure to reduce the volume of blood loss and replace as little as possible by transfusion. But much care must be taken not to lose more blood from the atrium at the time of releasing the occlusion of venae cavae.

Table III. Case of

No.	Name	Age	Sex	Cardio-thoracic ratio in X-ray	ECG	Right ventricular pressure mm. Hg.	Right atrial pressure mm. Hg	Systemic blood flow L./min.	Shunt of blood L./min.	Shunt / Syst. flow %
1	Y.M.	13	F	0.56	RVH, IRBBB	36/0	8/4.5	4.46	4.47	106
2	T.K.	29	F	0.52	IRBBB	38/2	5/0	4.58	8.84	193
3	Y.M.	16	F	0.68	IRBBB	53/3	3/-1	6.85	5.05	74
4	K.U.	14	F	0.54	IRBBB	34/-2	3/2	6.03	5.07	84
5	T.N.	33	M	0.52	IRBBB	48/5	6/2	5.52	1.84	33
6	R.K.	29	M	—	IRBBB	31/-2	5/1	2.60	3.60	138
7	Y.H.	13	F	0.58	IRBBB	55/0	16/0	3.23	3.70	115
8	M.T.	9	F	0.48	IRBBB	35/0	-2/-8	6.76	16.24	240
9	A.I.	12	F	0.54	RVH	43/0	8/4	4.34	5.06	133
10	K.F.	12	F	0.65	RVH, IRBBB	50/0	10/0	—	—	223
11	Y.K.	10	F	0.56	IRBBB	32/0	2/0	5.00	4.61	92
12	Z.K.	9	F	0.57	IRBBB	40/-3	7/2	2.60	0.82	32
13	H.K.	24	M	0.61	CRBBB	35/4	6/2	4.40	32.30	734
14	M.M.	9	M	0.71	RVH	67/0	12/0	—	—	94
15	S.S.	4	M	0.55	RVH	37/0	6/-1	—	—	65
16	S.O.	24	F	0.55	IRBBB	36/0	7/1	3.70	0.70	16
17	K.I.	23	F	0.53	RVH	50/-2	9/2	5.20	5.90	113

Clinical Experiences—

Atrial septal defect:

Operations on 17 cases of atrial septal defect have been performed closing the defect with continuous suture. All patients were completely cured (Table III). The cardiac occlusion times were from 3 min. 55 sec. to 12 min. and rectal temperatures at occlusion ranged from 24.2°C to 28.6°C. The sizes of defect were mostly 3 cm. to 4 cm. in the closed state but occasionally one was found to be as large as 7 cm. in diameter.

During the operation, the 10th case was accertained to be Lutembacher's syndrome and the narrow mitral valve was widened. The preoperative hepatomegaly of this patient disappeared several days after the operation.

During the operation of the 11th case, so much venous blood escaped from the atrium at removal of the air, that after releasing the occlusion not enough venous blood returned to the heart to fill it. At last the heart stopped and cardiac massage proved ineffective. Ventricullar fibrillation was artificially induced by injecting Norepinephrine into the left ventricle. But unexpectedly the instrument for electric shock was out of order, so we had to continue the cardiac massage, and simultaneously to rewarm intrathoracically until electric shock machine was repaired. Forty-three minutes passed from the beginning of cardiac occlusion to the onset of defibrillation. The

Atrial Septal Defect

Cooling	Rewarming	Occlusion time	Rectal temperature at occlusion °C	Size of defect diameter cm.	Type of defect	Result
Immersion	Intrathoracic+Blanket	4′35″	28.6	3.5	Ost. sec.	Cured
Immersion	Intrathoracic+Blanket	4′55″	26.9	3.5	Ost. sec.	Cured
Immersion	Intrathoracic+Blanket	5′40″	27.6	4.0	Ost. sec.	Cured
Air	Intrathoracic+Blanket	5′55″	24.2	4.0	Ost. sec.	Cured
Air	Intrathoracic+Blanket	6′40″	25.9	6.0	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	5′10″	25.5	5.0	Ost. sec.	Cured
Air	Intrathoracic+Blanket	5′54″	27.7	2.0	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	3′55″	26.0	1.8	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	12′00″	25.7	4.5	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	6′38″	25.5	4.0	Ost. sec. (Lutembacher)	Cured
Blanket	Intrathoracic+Blanket	5′36″	25.6	2.5	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	5′05″	26.6	4.0	Ost. prim.	Cured
Blanket	Intrathoracic+Blanket	7′00″	27.8	4.5	Ost. sec.	Cured
Blanket	Intrathoracic+Blanket	7′40″	27.0	3.5	Ost. sec.	Cured
Blanket	Intrathoracic	4′36″	26.4	2.5	Ost. sec.	Cured
Immersion	Intrathoracic+Blanket	6′11″	27.8	3.0	Ost. sec.	Cured
Immersion	Intrathoracic+Blanket	7′00″	29.8	7.0	Ost. sec.	Cured

patient awoke from anesthesia immediately after the operation and was found to suffer of no brain damage. It is difficult to say exactly how much circulation was maintained by cardiac massage, however, it was evident that the brain could withstand anoxia for a longer period of time than previously believed under the hypothermia.

Ventricular septal defect:

In operating on a ventricular septal defect, the ventricular wall must be insiced in order to open, and occlusion time must be prolonged since the ventricular wall must be closed with sutures before releasing the occlusion. In some cases the operation is further extended due to the fact that the defect must be closed with an Ivalon patch. Moreover, ventricular fibrillation is thought to be a frequent complication in the operation on the heart with myocardial damage. For this reason, hypothermia is generally thought not favorable for the operation of ventricular septal defect.

Although the data based on animal experiments is not quite suitable to be applied to clinical surgery, it is believed to be possible from the above mentioned results of animal experiments to perform the operation of ventricular sepatal defect under hypothermia if we used the precaution of rewarming intrathoracically.

All the 12 cases of ventricular septal defect operated on were com-

Table IV. Cases of

No.	Name	Age	Sex	Cardio-thoracic ratio in X-ray	ECG	Right ventricular pressure mm. Hg	Pulmonary arterial pressure mm. Hg	Systemic blood flow L./min.	Shunt of blood L./min.	Shunt / Syst. flow %
1	R.T.	20	F	0.48	LVH	27/-2	18/2	3.4	1.0	29
2	F.M.	7	F	0.44	Normal	33/2	19/6	5.3	2.0	38
3	H.M.	6	M	0.77	LVH	80/0	76/45	4.0	11.5	288
	(Reoperation)					75/0	65/20	—	—	64
4	K.O.	7	M	0.49	LVH	32/0	32/12	2.89	1.52	53
5	H.T.	5	M	0.50	LVH	34/0	29/12	—	—	46
6	H.U.	7	M	0.48	IRBBB BVH	60/0	30/8	—	—	60
7	T.K.	18	F	0.52	Normal	21/-2	13/4	4.54	1.36	30
8	T.E.	18	M	0.46	LVH	35/0	23/5	6.48	3.18	49
9	M.M.	7	M	0.50	IRBBB	27/0	20/5	3.7	2.3	62
10	N.T.	4	F	0.52	Norma	36/-10	28/7	—	—	62
11	T.T.	15	M	0.57	LVH	80/0	50/10	2.1	4.83	129
12	N.U.	12	M	0.46	IRBBB	33/0	30/8	5.3	6.3	119

pletely cured (Details are shown in Table IV). As the 3rd case had been completely cured after 2 successive operations of open heart surgery, we

Table V. Data of Catheterization

Ventricular septal defect, H.M., 6-year-old male

		27/Aug. (Before ope.)			11/Nov. (After 1st ope.)			20/Jan. (After 2nd ope.)		
		mm. Hg	Mean value	vol. %	mm. Hg	Mean value	vol. %	mm. Hg	Mean value	vol. %
Plum. Art.	Wedge	20/ 8	10					22/18	19	
	Hilum	76/45	58	9.7	60/22	38	12.8	25/ 7	13	12.8
	Bifurcation	76/45	60	9.0	65/20	38	14.7	25/ 7	14	
R. Ventricle	Infundibulum	80/ 0	43	9.4	75/ 0	28	14.5			13.6
	Center	76/ 0	33	8.7			15.0	40/-5	12	13.2
R. Atrium		13/ 5	7	4.0 6.2	2/-5	3	9.9 10.1	2/-5	-1	13.2 13.7
V.C.S.		14/ 6	6	5.0	3/-3	0	12.3	3/-5	-1	13.2
V.C.I.		7/ 4	5	5.4	2/-2	1	10.6	5/-5	0	12.3
Femoral Artery		10.0 (97.5%)			19.7 (99%)			17.1 (95%)		

Ventricular Septal Defect

Cooling	Rewarming	Method of closing defect	Occlusion time	Rectal temperature at occlusion °C	Size of defect diameter mm.	Result	Remarks
Blanket +Air	Intrathoracic +Blanket	Silk suture	6′27″	26.0	6	Cured	
Immersion	〃	Silk suture	6′20″	26.8	8	Cured	
Blanket	〃	Silk suture	8′05″	25.8	15	—	Cured after reoperation
Blanket	〃	Repair with Ivalon	13′30″	25.3		Cured	
Blanket	〃	Silk suture	8′18″	27.6	4	Cured	
Blanket	〃	Silk suture	6′15″	27.6	4	Cured	
Blanket	〃	Silk suture	12′25″	26.7	8	Cured	Left vena cava superior Used coronary perfusion
Immersion	〃	Silk suture	9′20″	27.4	5	Cured	Used coronary perfusion
Immersion	〃	Silk suture	8′40″	27.6	5	Cured	〃
Blanket	〃	Silk suture	6′22″	27.6	6	Cured	〃
Blanket	〃	Silk suture	8′10″	27.4	4	Cured	〃
Blanket	〃	Repair with Ivalon	13′05″	25.8	18	Cured	〃
Blanket	〃	Silk suture	7′25″	26.0	8	Cured	〃

would like to describe it in detail.

H. M., a 6-year-old boy, had been hospitalized with the chief complaint of frequent episodes of palpitation and precordial pain. Loud systolic murmur was heard over the whole precordium with its maximal intensity on the third left intercostal space, and a marked systolic thrill was felt. The second pulmonic sound was accentuated. The electrocardiogram showed left ventricular hypertrophy. The right ventricular pressure was as high as 80/0 mm.Hg, the pulmonary arterial pressure 76/45 mm.Hg and the cardiothoracic ratio by X-ray was as great as 0.77.

High ventricular septal defect of 15 mm. was closed with interrupted sutures under the direct vision. Suture proved to be inadequate for the large defect since the murmur was again heard several days after the operation. Reopening of the defect was accertained by a catheterization 2 months later

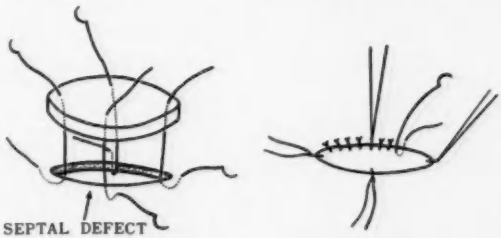


Fig. 3. Repair of defect with Ivalon patch.

Table VI. Cases of Ventricular

No.	Name	Age	Sex	Cardio-thoracic ratio in X-ray	ECG	Right ventricular pressure mm. Hg	Pulmonary arterial pressure mm. Hg	Systemic blood flow L./min.	Shunt of blood L./min.	Shunt / Syst. flow %
1	K.K.	10	M	0.50	RVH	103/4	15/5	2.92	2.81	96
2	T.T.	24	F	0.56	RVH	122/0	22/0	—	—	—
	(Reoperation)			0.64	BVH	83/0	62/10	2.27	10.06	443
3	M.H.	5	F	0.62	RVH	80/0	20/4	3.29	1.36	41
4	S.M.	23	F	0.47	BVH	120/0	22/4	4.81	r→l 0.59 l→r 0.16	

(Table V) and a reoperation was performed.

The right ventricle was opened on the scar of the previous operation. As the defect was found to be completely reopened, an Ivalon patch was fixed with 14 interrupted sutures to repair the defect (Fig. 3). The cardiac occlusion time required for this operation was 13 min. 30 sec. (Fig. 4). The patient recovered more quickly after the second operation than the first. He was completely cured and able to leave the hospital.

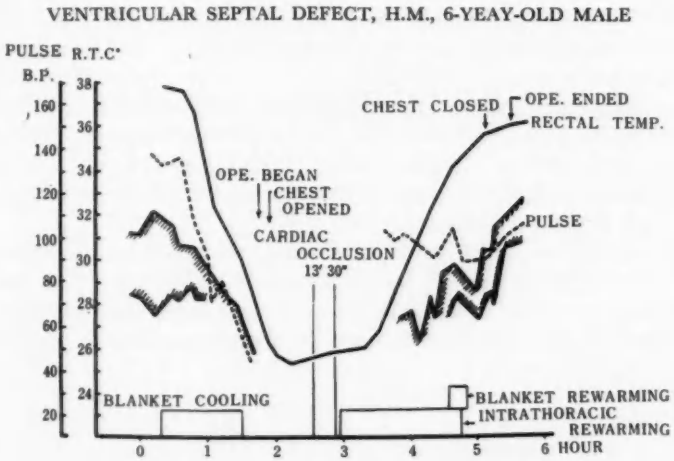


Fig. 4. Body temperature, pulse and blood pressure during operation.

As mentioned above, the brain has been found to tolerate anoxia for longer period than previously expected, accordingly myocardial anoxia would become more significant at circulatory occlusion under intermediate hypothermia. Hence we apply coronary perfusion with oxygenated heparin-

Septal Defect with Pulmonary Stenosis

Cooling	Rewarming	Occlusion time	Rectal temperature at occlusion °C	Method of operation	Size of defect diameter mm.	Result	Remarks
Immersion	Intrathoracic +Blanket	9′18″	26.2	Silk suture +Valvulotomy	6	Cured	
Blanket +Air	〃	5′55″	27.6	Valvulotomy	—	—	Cured after reoperation
Blanket	〃	14′07″	27.0	Repair with Ivalon	18	Cured	
Blanket	〃	14′39″	27.5	Silk suture+Excision of crista	10	Cured	
Immersion	〃	14′55″	27.3	Silk suture +Excision of thickness on the infundibulum	7	Cured	

ized blood for the operations in which occlusion time is expected to be prolonged and have obtained satisfactory results. When coronary perfusion is started at the end of repairing the defect, it does not disturb the surgical manipulation and the returning blood to the ventricle serves to drive out the air.

In the 6th case in which the coronary perfusion was employed, normal rhythm continued for as long as 14 min. 39 sec. during the occlusion.

Ventricular septal defect with pulmonary stenosis:

Operations were performed on 4 cases of ventricular septal defect with pulmonary stenosis. The details are shown in Table VI.

The 2nd case, T. T., a 24-year-old female, complained of shortness of breath and cyanosis after exertion for the past few years. Precordial pain was especially pronounced for the last 2 years.

A loud systolic murmur was heard over the entire precordium. Its maximal intensity was at the pulmonic area, and a systolic thrill was also felt but the second pulmonic sound was hardly heard. An X-ray revealed normal shape of the heart and cardio-thoracic ratio was 0.56. Pulmonary stenosis was ascertained to be a valvular type by a selective angiocardiogram in the right ventricle and also by pressure tracing taken during withdrawal of the catheter from pulmonary artery into the right ventricle. Oxygen saturation slightly increased at distal to the bifurcation of the pulmonary artery.

Valvulotomy was performed by cutting a funnel-shaped valve 3 ways through the main pulmonary artery opened longitudinally. By this operation no infundibular stenosis, aortopulmonary defect and patent ductus arteriosus were found and as no arterial blood flowed from the right ventricle, the disease was believed to be a pure pulmonary valvular stenosis.

An obstinate cough appeared a week after the operation and gradually became worse, and at last uncontrollable even with intensive medication. An

Table VII. Data of Catheterization

		13/May (Before ope.)			18/Jan.(After 1st ope.)			14/Mar. (After 2nd ope.)		
		mm. Hg	Mean value	vol. %	mm. Hg	Mean value	vol. %	mm. Hg	Mean value	vol. %
Pulm. Art.	Wedge				37/10	19		4/0	1	
	Hilum	14/ 2	69	12.5	44/ 4	21	19.3	9/2	4	14.1
	Bifurcation	22/ 0	7	12.5	62/10	27	19.6	24/3	12	14.4
R. Ventricle	Infundibulum			11.5			20.3			13.9
	Center	122/0	20	11.1	83/ 0	35	20.0	45/0	14	13.9
R. Atrium				10.9	16/ 8	12	11.5	4/−1	1	13.9
							12.0			14.1
V.C.S.		2/ 0	1	11.8	20/10	14	11.0	3/−1	1	13.9
V.C.I.					16/10	14	12.0	6/0	3	14.4
Femoral Artery		15.5 (95%)			21.3 (98%)			16.8 (92%)		

X-ray revealed the engorged branches of pulmonary artery and cardio-thoracic ratio increased to 0.66. As a still high right ventricular pressure and a marked left to right shunt were proved to exist by the catheterization (Table VII), reoperation was performed.

As the main pulmonary artery could not be separated from the pericardium in sinus transversus pericardii, only the circulation of the aorta was occluded and that of the pulmonary artery left intact. The Ivalon patch was employed to close the high ventricular septal defect of 18 mm. × 15 mm., which was fixed with 18 interrupted sutures. After releasing the occlusion the heart stopped. Ventricular fibrillation occurred, but was checked soon (Fig. 5).

Shortly after the second operation, the physical findings and results of the laboratory examinations have improved and the complaints have com-

Table VIII. Cases of

No.	Name	Age	Sex	Cardio-thoracic ratio in X-ray	ECG	Right ventricular pressure mm. Hg	Pulmonary arterial pressure mm. Hg	Systemic blood flow L./min.	Shunt of blood L./min.	Cooling
1	Y.I.	27	F	0.60	RVH	115/−5	12/8	6.4	r→l 2.2	Immersion
2	T.K.	6	F	0.54	RVH	76/8	9/5	2.8	l→r 1.6	Blanket

VENTRICULAR SEPTAL DEFECT+PULMONARY STENOSIS
T.T. 24-YEAR-OLD, FEMALE

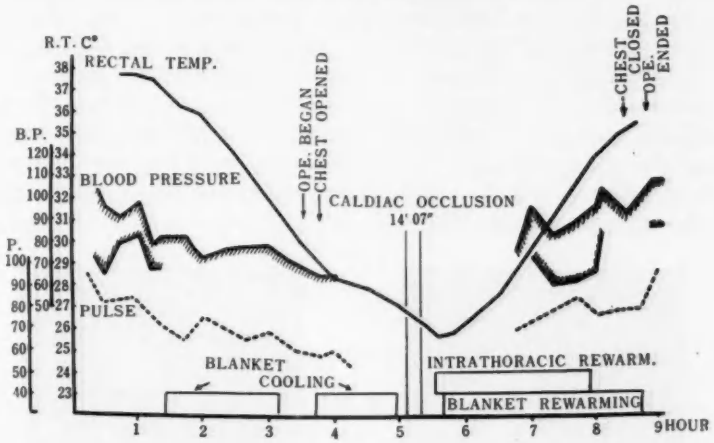


Fig. 5. Body temperature, pulse and blood pressure during operation.

pletely disappeared.

The 4th case, S. M., a 23-year-old female, had a ventricular septal defect with infundibular stenosis. Catheterization revealed right to left shunt. The operation was further complicated by the fact that the heart muscle had become so fragile and it was torn by a thumb forcept and a thread during the operation. The occlusion time was also prolonged to 14 min. 55 sec. Ventricular fibrillation which occurred after releasing the occlusion was easily corrected by intrathoracic rewarming.

Tetralogy of Fallot:

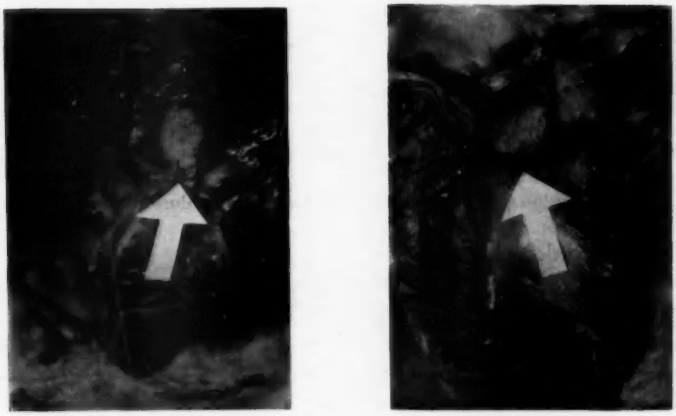
As in Table VIII, operations were performed on 2 cases of tetralogy of Fallot with unsuccessful results.

In the 1st case, Y. I., a 27-year-old female, the left to right shunt was not proved by catheterization and the right to left shunt was not clear on

Fallot's Tetralogy

Rewarming	Method of Operation	Occlusion time	Rectal temperature at occlusion °C	Size of defect diameter mm.	Results
Intrathoracic	Valvulotomy	10′28″	27.8		
+Blanket	Repair of defect with Ivalon	13′05″	27.0	25	Died 6 days after operation due to pulmonary edema
〃	Repair of defect with Ivalon +Excision of thickness on the infundibulum	12′28″	27.0	20	Died suddenly 56 hours after operation by unknown cause

the angiocardiogram. However, as the pulmonary stenosis was proved to be of the valvular type, we first performed valvulotomy through the pulmonary artery, and at the same time found a ventricular septal defect. In the 2nd cardiac occlusion, the right ventricle was opened and the high ventricular septal defect of 25 mm. × 20 mm. was repaired with a Ivalon patch. On the 5th postoperative day spontaneous pneumothorax occurred and the patient died on the next day. Post-mortem examination disclosed that there had been an overriding aorta, a thin left ventricular wall and the Ivalon patch completely adhered to the septum, the surface of patch being smoothly covered with endothelium (Fig. 6).



from right side from left side

Fig. 6. An arrow shows Ivalon patch which completely adhered to the septum and smoothly covered with endothelium.

In the 2nd case, T. K., a 6-year-old female, despite the fact that the angiocardiogram showed a marked right to left shunt, cyanosis and clubbed fingers were not prominont on physical examination. The arterial blood indicated 97% saturation. Thickened crista supraventricularis was removed and high ventricular septal defect was closed surgically with the Ivalon patch. The left ventricle was so small that it was completely hidden behind the right ventricle. The pulmonary artery was so small in diameter and was only one third of the aorta. The patient awoke from anesthesia and was able to take liquid food, but died suddenly 56 hours after the operation by an unknown cause.

Although the cause of death in these 2 cases was not clear, we can not believe these were the side effect of hypothermia. As a left to right shunt exists in ventricular septal defect, the left ventricular work increases abnormally and the right ventricle must become accustom to the high pressure. After the closure of the defect there is only a essential systemic flow from the left

ventricle, and no necessity for the right ventricle to adjust. The activity of both ventricles decreases after the operation. However, as a right to left shunt exists in tetralogy of Fallot, there is a necessity for the right ventricle to adjust to high pressure and pump out more blood by shunt volume. At the same time there is, for the left ventricle, a less than the normal output by shunt volume. Actually the left ventricle of tetralogy of Fallot is very small. Therefore, after the radical operation the left ventricular work markedly increases and can no longer adjust to the increased work.

Recently if a small left ventricle or a small pulmonary artery is found, we consider the radical operation is feasible, otherwise we perform Blalock's operation.

Discussion

For open heart surgery, both hypothermia and extracorporeal circulation have been employed. As these methods have advantages and disadvantages, these methods should be employed according to their individual characteristic. For the operation which can be performed with the short occlusion time, hypothermia which causes less stress than extracorporeal circulation should be used.

Ventricular fibrillation which was thought to be the most important complication of hypothermia can be prevented by careful selection of the drugs for anesthesia and proper use of prostigmine. When it occurs, fibrillation is checked by the intrathoracic rewarming. We encountered ventricular fibrillation in 4 cases of advanced lesion, all of whom were over 24 years old, but of course it was readily stopped (Table IX).

Table IX. Occurrence of Ventricular Fibrillation and Cardiac Arrest

Number → Anesthesia ↓	Operation	Cardiac arrest		Ventricular fibrillation
Ether	38	7	1	24-year-old female, VSD+PS Myocardial damage (##)
N_2O	5	1	3	24-year-old female, VSD+PS Arrest → Fibrillation 27-year-old female Fallot's tetralogy Occurred before occlusion Prostigmine had not been used 24-year-old male, ASD Much blood lost at incision
Total	43	8	4	

We have performed 43 operations on a total of 41 patients and completely cured all but 2 cases of tetralogy of Fallot (Table X).

We have cured 2 cases with ventricular septal defect by reoperations, indicating that intrathoracic rewarming enables the surgeon to carry out a

Table X. Total Cases Operated under Hypothermia

Diseases ↓ / Number →	Case	Operation	Death
Atrial septal defect	17	17	0
Ventricular septal defect	12	13	0
Ventricular septal defect+Pulmonary stenosis	4	5	0
Tetralogy of Fallot	2	2	2
Aortic stenosis	1	1	0
Pulmonary stenosis	2	2	0
Coarctation	2	2	0
Aneurysm of ascending aorta	1	1	0
Total	41	43	2

reoperation with no fear or hesitation.

The safe time limit for cardiac occlusion was generally considered to be about 10 minutes under intermediate hypothermia. However, the brain has been found to tolerate anoxia for longer period than previously expected. Employing a coronary perfusion, it is possible to prolong the occlusion time indirectly because of prompt recovery of effective cardiac output after releasing occlusion. At present, the safe time limit is believed to be about 15 minutes. The operation such as ventricular septal defect with pulmonary stenosis, which requires about 15 minutes of cardiac occlusion can be performed by hypothermia.

Summary

(1) It would be physiological to keep the temperature of the thoracic region higher than that of the body surface under hypothermia. This consequently would exert a favorable influence on the general circulatory condition. Therefore it would be reasonable to cool from the body surface and rewarm it from the thoracic cavity. We had always used the intrathoracic rewarming.

(2) We proved in the animal experiments that hypothermia could safely be applied even to the subject with damaged myocardium when we employed intrathoracic rewarming.

(3) Ventricular fibrillation was prevented in almost all cases by selecting the drugs for anesthesia and proper use of prostigmine, and, when it did occur, was easily stopped by electric shock.

(4) We had performed 43 operations on total of 41 patients and completely cured all but 2 cases of tetralogy of Fallot.

(5) The safe time limit for cardiac occlusion under intermediate hypothermia is believed to be about 15 minutes.

Addendum

After this article was prepared for publication, we performed an operation on

a 12-year-old male with ventricular septal defect combining pulmonary hypertension. Because of anatomical difficulty in applying Ivalon patch, cardiac occlusion required 20 minutes, while rectal temperature was 26.5°C. Postoperative recovery was quite uneventful. This experience of ours suggests that the safe limit of cardiac occlusion can be extended to 20 minutes.

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The Study on Plethysmocardiography
A Preliminary Report

Hiroto MASHIBA, M.D.

An attempt to research mechanical events of the cardiac cycle, contraction and relaxation, not partially as roentgen-kymography or electro-kymography, but as a whole, was proceeded by application of principles of plethysmography and indirect roentgenography. An activating cardiac shadow on the fluorescent plate of fluoroscopy was converged on phototube by a lens. For diminishing the influence of intensity changes of X-ray beam, two phototubes were used in a balanced circuit. The difference of the phototube currents was practically entirely related to the absorption variations of the patient and fluctuation of the current was related mostly to the volume of the intracardiac blood. In this experiment, the curve obtained was analysed qualitatively. This new method to investigate the cardiac function, plethysmocardiography, is probably applicable to physiological and clinical examination.

EACH method which has been used in the clinical determination of the function of the cardiovascular system possesses of its own significance and utility. The clinico-physiological studies of the heart consist of electrophysiology and hemodynamics, the former depends mainly, for its clinical significance, on electrocardiography which awaits further clinical interpretation and basic research, and the latter on intracardiac catheterization which invariably requires a surgical aid. The cardiac movements which are recorded by roentgen-kymography and electrokymography are only the partial movement of the heart. But the systolic movement converged, becoming intricately mixed oscillatory and rotatory movements, does not make sufficiently clear the dynamic phase of the heart beat. The mechanical movement and the hemodynamics of the heart and the relation between the cardiac movement and the peripheral circulatory condition can hardly be explained without the information to be gained by recording continuously the manner of the whole cardiac work in its systole and diastole.

Method

Fig. 1 illustrates the principles on which the cardiometrical method is based and the apparatuses used*; current A-B flows continuously and in an invariable

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* The apparatus used; an X-ray generator (Polydor, Siemens), a roetgen tube (F.D.O.-63,

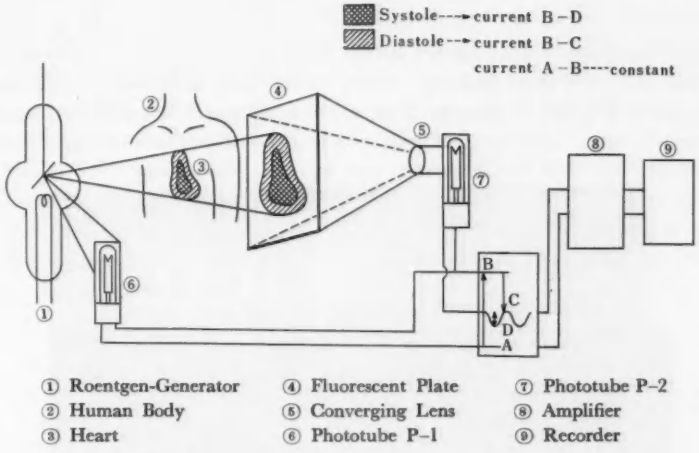

Fig. 1. The schematic illustration of the apparatuses.

amount through the phototube P–1, which received on the fluorescent paper pasted on it, the X-ray entering it directly from the X-ray tube; the fluorescent plate is quite dark and admits a decreased current B-C or is bright and admits an increased current B-D, according to the dilatation of the heart being filled with blood or to the contraction of the heart leaving little blood in it. When P–1 and P–2 are connected as in Fig. 1, current B-C is equal in volume to the X-ray absorbed by the chest wall, lungs, mediastinal cavity and by the wall of the heart; the current changing in amount in relation to this invariable amount of the X-ray undergoes another quantitative change as the blood in the heart and the great vessels fluctuates in volume, and current C-D shows the cardiac output. This current changing in value, when amplified and recorded, forms a curve to be described later.

The shadow cast by the heart on the central part of the fluorescent screen undergoes some change in size as the heart beats, which, depending on the amount of the X-ray reaching the screen, is composed of not only a change in shape on the frontal surface but also a change in thickness on the sagittal surface. The change in the amount of the X-ray reaching the screen is ascribable mainly to the change that the heart produces as it contracts and dilatates in the volume of blood existing in the heart and the major vessels. Accordingly, the current into which the changing brightness of the screen is converted in a phototube, when determined in a galvanometer, amplified and recorded, denotes the change occurring in the amount of blood contained at the same time in the heart and the great vessels.

The cardiometry, which is based on indirect roentgenography and electrokymography and by which the change occurring in the volume of the heart is graphycally traced, led to the result described below.

Toshiba), a fluorescent plate (F. 4, Kyokko), a converging lens (Canon F–1.8, f–35 mm.), phototubes (P–1; RCA 931–A, P–2; RCA 1P21), and amplifier and resister (Electrokymograph, Mingograph–42, Elema).

Result

Fig. 2 is from a normal person, a 24-year-old healthy female, with no detectable vascular abnormality. Two curves from the subject, one (above) E.C.G. (lead–II) and the other (below) tracing the heart volume, appeared at the same time. The appearance of the P-wave and of the QRS-complex was followed by that of the waves tracing the ventricular contractions, the latter waves were similar in form to those tracing the changing volumes from the dog ventricle[1] and normal ventricular curve of an electrokymogram,[2] and the T-wave terminated when each ventricular contraction had reached its acme.

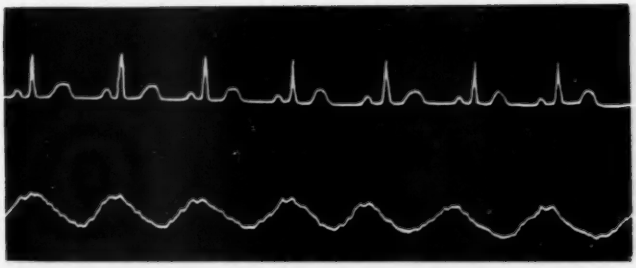

Fig. 2. A normal case.

Fig. 3 is from a patient with a cardiac disorder, a 26-year-old female, with clinical symptoms of mitral stenosis and regurgitation. The heart action was traceable from E.C.G. (lead–II). Two traceable ventricular extrasystoles, which occurred in no time to a normal ventricular contraction, had a prolonged systole occurring between normal contractions. Another ventricular contraction traced from this patient reached its acme sooner than a corresponding contraction from a normal person.

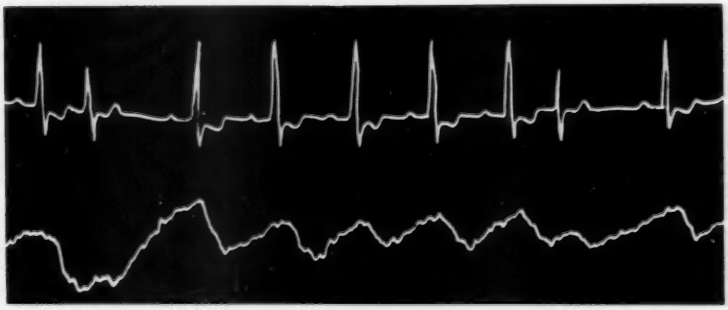

Fig. 3. A Patient with mitral stenosis and regurgitation.

Fig. 4 is a tracing from a 22-year-old female, in whom an intracardiac

catheterization confirmed the presence of patent ductus arteriosus. E.C.G. of lead II revealed no abnormality in this patient but the heart volume traced simultaneously showed that a small characteristic contraction presumably indicates the contraction and dilatation of the major vessels and appeared between the middle of a normal systole and the end of an accessory normal diastole, i.e. before the appearance of a P-wave.

Fig. 4. A patient with patent ductus arteriosus.

Discussion

Approximately 160 ml. of blood sent out and taken in each cardiac cycle by the heart is naturally accompanied by corresponding variation in the amount of the X-ray to be absorbed within a human body under X-ray examination and by a consequent variation in the brightness of the fluorescent plate. This variation, recorded continuously for a certain period, may reasonably be expected to serve as a valuable metrical means of medical research. E.C.G. from a normal person gave as a whole a satisfactory record of the ventricular systole bearing a particular resemblance to the electrokymographycal record of the same movement. As may naturally be expected a small-sized wave appearing in the record of each systole was unanalysable but the arterial and venous activity was a probable factor in its appearance. Calibration of voltage remained as another unsolved problem, and the cardiac output, an important problem in its own way, was left unexamined in this experiment, as mentioned in the beginning of this paper. The changing volume of the first case was examined with a view to observe the waves tracing extrasystoles. The result reached gave a key to the quantitative analysis of such waves and made it possible to determine without the aid of E.C.G. extrasystole, atrial fibrillation and the coincidental dynamic phase of the blood in circulation. The changing heart volume in the second case was examined to evaluate the diagnostic value of the present method. It was found as a result that a small characteristic wave tracing a systole and appearing between a T-wave and a P-wave was of high clinical significance, provided it was invariably traceable from a patient with patent ductus arteriosus. Two technical problems awaiting

further investigation are how to adjust the calibration voltage and how a wave-length specific to the fluorescent plate is related to a wave-length specific to the phototube. The dynamic phase of the blood supplying the head and the extremities which was considered in this experiment, will also be applied for diagnostic purpose.

It is the author's intention to examine this method in more detail for its improvement.

Summary

(1) A new method by which the changing volume of the heart can be recorded was devised for continuous observation of the heart as a whole.

(2) The principle on which the method is based was explained and the apparatuses used were described.

(3) The auricular and ventricular contractions in a normal case were accurately traceable by this method.

(4) Extrasystoles in a patient with mitral stenosis and insufficiency were recorded as corresponding abnormal contraction.

(5) Peculiar waves probably indicative of contraction of the major vessels, were recorded from a patient with patent ductus arteriosus.

(6) The experimental and diagnostic significance of this method seems to be nearly settled by the above described informations obtained by it.

(7) More detailed examination of this method and its improvement are being attempted.

(This study was reported in summary on May 31, 1959, at the 6th annual congress of the Kyushu Branch of the Japanese Circulation Society.)

Acknowledgements

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Electrocardiographic Changes in Open Heart Surgery under Hypothermia

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In 37 patients with congenital heart disease who underwent the open heart surgery under hypothermia, electrocardiographic tracing was recorded throughout the entire course of hypothermia and surgery.

R-R, P-Q, QRS and Q-T intervals were progressively prolonged with cooling, shortened with rewarming, and recovered to preoperative values with the returning of the body temperature to the normal. In a few cases, ST elevation was observed during cooling process. Various arrhythmias including ventricular fibrillation were prone to occur in adults or severe cases compared with in children or mild cases. However, they were reversible, and ventricular fibrillation which has been regarded as one of the most troublesome complications was eliminated easily by intrathoracic rewarming.

IT has been generally accepted that hypothermic method for open heart surgery may be applied only for the repair of atrial septal defect or pulmonary valvular stenosis with or without atrial septal defect, since ventricular fibrillation is prone to be caused by ventriculotomy at lowered temperature.

Swan[1] and Derra reported their excellent clinical results of the operation for atrial septal defect and pulmonary valvular stenosis, and described that atrial septal defect (ostium secundum) and pulmonary valvular stenosis could be corrected very safely and perfectly with the aid of hypothermia. They concluded that an artificial heart-lung apparatus was not needed in cases of atrial septal defect or in pulmonary stenosis, but ventricular septal defect might not be operated successfully with hypothermic method alone. On the other hand, according to our experimental result on deep hypothermia,[2] we believed that when intrathoracic rewarming method is used, the resuscitation of fibrillatory heart is very easy and satisfactory, and the use of the hypothermia for the operation of ventricular septal defect and other cardiac anomalies may be quite possible.

In our surgical clinic, as shown in Table I, 17 cases of atrial septal defect (A.S.D.), 12 of ventricular septal defect (V.S.D.), 4 of pulmonary stenosis with ventricular septal defect (P.S.+V.S.D.), one of pure pulmonary valvular stenosis (P.S.), one of aortic valvular stenosis (A.S.) and 2 of tetralogy of

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Table I. Cases Operated by Hypothermic Method

	Case number	Dead case
A.S.D.	17*	0
V.S.D.	12	0
P.S.+V.S.D.	4	0
Tetralogy of Fallot	2	2**
A.S.	1	0
P.S.	1	0

* One case of Lutembacher's syndrome is included.

** One case died from pulmonary edema on 7th postoperative day. The other case died from unknown cause on 2nd postoperative day.

Fallot were operated by hypothermic method. Operations were successful in all cases, except in 2 cases of tetralogy of Fallot, one of which died from pulmonary edema on the 7th postoperative day and another from unknown cause on the 2nd postoperative day (Table I).

Since arrhythmia, particularly the ventricular fibrillation is prone to result from anesthesia and cooling in diseased heart, continuous observation of electrocardiogram is necessary throughout the entire processes of open heart operation under hypothermia. In this paper, the changes in pattern of electrocardiogram which appeared on the process from the beginning of the cooling to the establishment of rewarming during the operation of the congenital heart diseases, will be investigated and the relationship between the changes and clinical data will be discussed.

Materials and Method

A total of 37 cases as described above were studied in this study.

After endotracheal intubation, patients were anesthetized with ether to the 2nd or 3rd plane of 3rd stage, and when ether anesthesia was impossible due to the fall of blood pressure or appearance of remarkable arrhythmia, N_2O was used in combination with muscle relaxant.

Patients were cooled by the immersion in ice water bath, on a blanket saturated with ice water or in a thermo-box to about 30°C of rectal temperature so that lowest temperature of rectum reached about 27°C due to drifting. The lowest rectal temperature in this series of the heart surgery ranged between 28.6°C and 24.5°C. Thoracotomy was performed bilaterally or unilaterally through the 4th intercostal space and in- and outflow were occluded. Immediately after the occlusion of outflow, 1 or 2 ml. of 0.025% prostigmine was injected into coronary arteries through the basis of aorta.

In 5 cases, Ivalon patch was attached for the closure of ventricular septal defect and in other cases, defects were closed by suture. Stenosis was relieved by valve plastic and conus plastic. During the intracardiac manipulation, coronary perfusion with heparinized anu oxygenated blood was made through the transfusion

needle which was inserted into the basis of aorta in 23 cases of this operation series. Period of circulatory interruption ranged between 3′55″ and 14′55″.

After the release of in- and outflow occlusion, intrathoracic rewarming was started. Warm water of about 40°C was poured continuously into the thoracic cavity and the water which retained in the posterior part of this cavity was suctioned. After the temperature was raised to about 34°C the intrathoracic rewarming was stopped and patients were rewarmed by blanket which was saturated with about 40°C warm water and applied under the patient, while the thorax was closed. In one case of tetralogy of Fallot, circulatory interruption was performed twice with an interval of about 15 min. (first 10′30″, second 13′45″).

Electrocardiogram was continuously observed on dual beam oscilloscope, and recorded at every 2°C decrease or increase in body temperature and whenever a change of electrocardiogram appeared.

Results and Discussion

The Influence of Ether Inhalation on the Heart with Anomalies—

Although as shown in Table II, in some cases the operation had to be postponed or N_2O had to be used instead of ether, because of the occurrence of serious arrhythmia and the fall of blood pressure, we have arrived an opinion through the experiment on deep hypothermia, that when hypothermia is employed, deep ether anesthesia should be used, whatever the type of operation may be, because ventricular fibrillation and arrhythmia occur rarely in ether anesthesia compared with in barbiturate alone.[3] On the other hand, there have been some reports concerning the fact that ether anesthesia might give more influence on diseased heart than on normal heart.

Table II. The Influence of Ether Inhalation on Diseased Heart

Remarkable ventricular extrasystole:

A.S.D. (30y); Occurred before cooling. Operation was postponed to another day. N_2O was used.

A.S.D. (22y); Occurred during cooling (35°C). Operation was performed on another day under ether anesthesia.

V.S.D. (9y); Occurred before cooling. Operation was given up.

Atrioventricular dissociation:

A.S.D. (13y); The plan for operation was not changed.

V.S.D. (7y); The plan for operation was not changed.

Fall of blood pressure:

Tetralogy of Fallot (28y); The operation was performed on scheduled day under N_2O anesthesia with muscle relaxant instead of ether.

P.S.+V.S.D. (24y); The operation was performed on scheduled day under N_2O anesthesia with muscle relaxant instead of ether.

A.S.D. (24y); The blood pressure fell with a little additional inhalation of ether during cooling (34°C). The operation was postponed to another day. N_2O was used.

For the prevention of these complications, it is important to anesthetize patient gradually with the low concentration of ether.

As shown in Fig. 1, N_2O was used in patients above 20 years of age and it may be considered that myocardium of patients above 20 years of age is more damaged and more sensitive to ether than that of patients below 20 years.

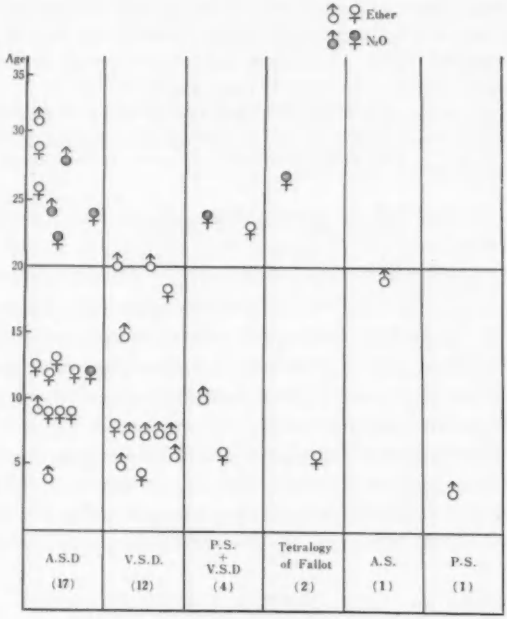


Fig. 1. The age of patient and the anesthesic agent used.

The Changes in R-R, P-Q, QRS and Q-T Intervals during Cooling and Rewarming—

The R-R, P-Q, QRS and Q-T intervals were progressively prolonged with lowering of body temperature, again shortened with rising of body temperature and recovered to normal range of these values, but the feature of these changes varied in each patient and was not always regular. Perhaps, the feature of these changes may depend on the individuality of patient, the depth of anesthesia, the kind of anesthetic agent used, the rate of lowering or rising of body temperature and many other factors, and it was difficult to decide which factor most significantly resulted in the changes of these intervals.

P-Q interval exceeding 0.35 sec. was observed in 2 cases and shortening below 0.10 sec. in 2 cases.

The prolongation of Q-T interval was especially remarkable and Q-T ratio calculated from Bazzet's formula was increased progressively with lowering of body temperature (Fig. 2).

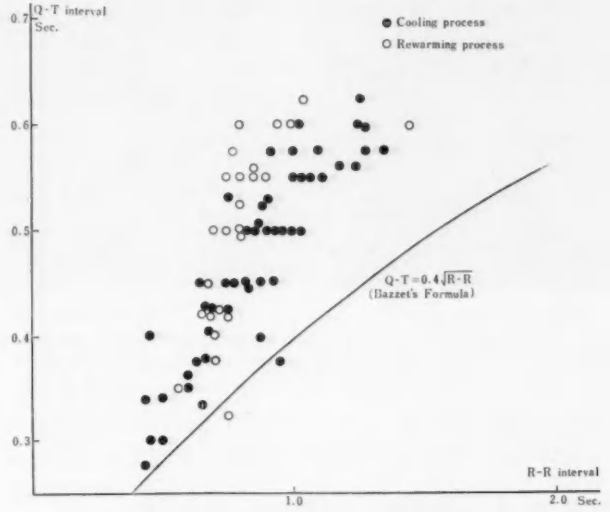


Fig. 2. The relationship between R-R and Q-T.

QRS interval naturally showed a marked prolongation when right bundle branch block occurred after the suture of ventricular septal defect.

The Changes in ST-T—

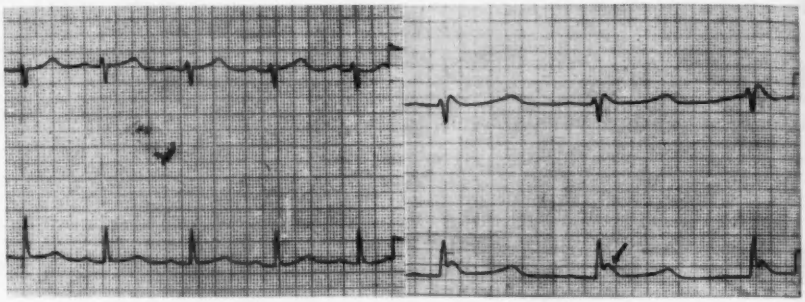
No definite tendency of the changes in ST-T was found during cooling and rewarming.

In a few cases, the ST elevation appeared as a particular change in hypothermia. The term " current of injury ", " injury potential " or " injury current " has been given to this change by Osborn[4] and Covino.[5] This so called " current of injury " had various amplitude, width and form, and was roughly classified into 2 groups.

One is the ST elevation which takes off at the descending part of R-wave, and the other is small wave which appears closely following QRS-complex. In Fig. 3, the typical " current of injury " which belongs to the former is shown.

Osborn[4] and Covino[5] attributed the appearance of this wave to the blood acidosis and hypercapnia, but Santos[6] and Jude[7] denied the relationship between this wave and acidosis or hypercapnia. Angelakos[8] regarded the increase of serum Ca^{++} as an important factor for the appearance of this wave. We recognized experimentally that the increase in serum Ca^{++} was more significant than the hypercapnia. Osborn, Covino and Angelakos in experimental animals and Boba[1] clinically recognized that when this ST change appeared, the ventricular fibrillation was prone to occur.

The patient who had " current of injury " shown in Fig. 3 was tetralogy



a) Preoperative b) Rectum temp. 30°C

Fig. 3. An example of so called " current of injury " in a 28-year-old female with tetralogy of Fallot anesthetized with N_2O.

of Fallot anesthetized with N_2O, and this was only a case which developed ventricular fibrillation before circulatory interruption.

The Arrhythmia and the Disturbance in Stimulus Conduction—

The character and the incidence of the arrhythmia and the disturbance of the conduction observed during this series of open heart surgery are summarized in Table III.

Table III. The Arrhythmia and the Disturbance of Stimulus Conduction*

P-Q prolongation (0.35 sec.)	2 cases
P-Q shortening (0.10 sec.)	2
Wandering pace maker	4
A-V dissociation	13
Atrial fibrillation	9
Atrial flatter	1
Nodular rhythm	6
Bigeminy	2
Remarkable ventricular extrasystole	3
Right bundle branch block	7
Cardiac arrest	9
Ventricular fibrillation	7

* Ventricular fibrillation and cardiac arrest are not included, and the arrhythmia observed during intracardiac manipulation is not described in this table.

Right bundle branch block:

The right bundle branch block was observed in 7 cases and it appeared after the closure of ventricular septal defect at the time of the rewarming process in the cases of V.S.D., P.S. with V.S.D. and tetralogy of Fallot.

The duration of its appearance was from 30 min. to 50 hours. The mean diameter of septal defect was 13.8 mm. in the cases with right bundle

branch block and 6 mm. in those without right bundle branch block. It may be considered then that the right bundle branch block may be caused by temporary occurrence of edema in conduction system due to the ligature of tissue around the defect (Table IV).

Table IV. Right Bundle Branch Block

1)	The stage of occurrence:	
	All occurred after the suture of ventricular septal defect.	
2)	The duration time:	
	Over 24 hours	1 case
	5 to 10 hours	1 case
	Below 1 hour	5 cases
3)	The mean diameter of ventricular septal defect in	
	cases with right bundle branch block	13.8 mm.
	cases without right bundle branch block.	6.0 mm.
4)	The distribution of diseases:	
	V.S.D.	4 cases
	P.S.+V.S.D.	1 case
	Tetralogy of Fallot	2 cases

Ventricular fibrillation:

The ventricular fibrillation appeared in a total of 10 occasions in 7 cases. The ventricular fibrillation occurred during cardiac manipulation or immediately after the release of circulatory interruption except in one case of tetralogy of Fallot in which it occurred twice before circulatory interruption. Except one case in which it continued for 18 min., it could be eliminated easily in a few minutes by intrathoracic rewarming and electric shock.

The ventricular fibrillation has been recognized as one of the most troublesome complications, and it has been said that the occurrence of ventricular fibrillation depends on many factors, for example, the increased irritability of the heart muscle at lowered temperature, the length of the period of circulatory interruption, the type of the cardiac anomalies, the grade of the damage of the heart muscle, the type of anesthetic agent used and the change in blood pH and serum electrolyte. In our cases, ventricular fibrillation was prone to occur in serious cases above 20 years of age with the remarkable abnormalities of hemodynamics and severely damaged myocardium, in N_2O anesthesia and after the circulatory interruption for over 10 min. with a few exceptions (Table V and Fig. 4, 5).

For the prevention of ventricular fibrillation, the injection of prostigmine to coronary arteries and the coronary perfusion with arterialized blood were made. Although they were very useful for the reduction of anoxia of cardiac muscle during circulatory interruption and defibrillation, the result was not quite excellent.

DiPalma[10] reported that the elimination of fibrillation in hypothermia became easy by pouring warm water on fibrillating heart and Blades and

Table V. Ventricular Fibrillation

1)	The stage of occurrence:		
	Before circulatory interruption	1 case	2 times
	During intracardiac manipulation	3 cases	5 times
	Following cardiac arrest which occurred during circulatory interruption	3 cases	3 times
2)	The duration time:		
	Longest	18′50″	
	Shortest	45″	
3)	The distribution of diseases:		
	A.S.D.	1 case	
	V.S.D.	3 cases	
	P.S.+V.S.D.	2 cases	
	Tetralogy of Fallot	1 case	
4)	The age:		
	Over 20 years of age	5 cases	
	15 years of age	1 case	
	7 years of age	1 case	
5)	The anesthetic agent:		
	Ether	3 cases	
	N_2O	3 cases	

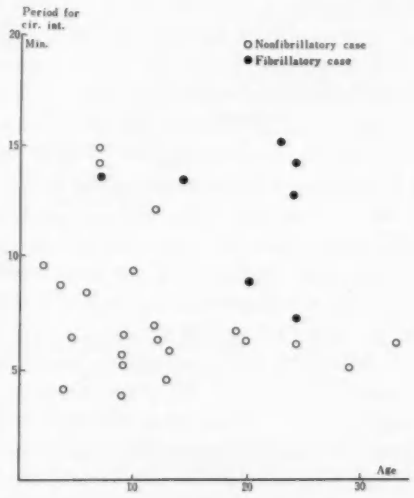


Fig. 4. The age of patient, the period for circulatory interruption and the ventricular fibrillation.

Pierpont[11] clinically used intrathoracic rewarming for the first time. Müller[12] reported that the ventricular fibrillation which occurred in open heart surgery in hypothermia could be easily eliminated by intrathoracic rewarming.

In our cases, as above described, the ventricular fibrillation occurred in

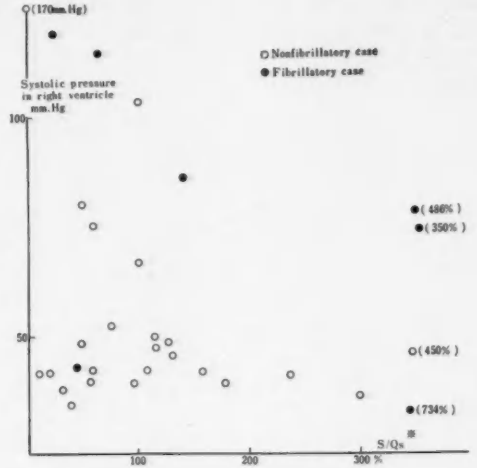


Fig. 5. The preoperative hemodynamics and the ventricular fibrillation.

S: Intracardiac shunt volume for 1 min.
Qs: Systemic flow volume for 1 min.
S/Qs: The ratio of the shunt to the systemic flow.

7 cases, but the defibrillation was possible in all cases by intrathoracic rewarming without any untoward effects, and the anomalies were successfully corrected. We believe that when the condition of the heart is not extremely impaired, the ventricular fibrillation in hypothermia can be eliminated and the circulatory interruption is possible for about 20 min. at 28°C as asserted by Wittenstein and Grow.[13] In view of the fact that the ventricular fibrillation occurs more commonly in adults, the operation is advisable at as young as possible.

Cardiac arrest:

Cardiac arrest was observed in 9 cases and was seen during the circulatory interruption. In general it was reversed to the normal beat after the cardiac massage for 50 sec. to 2 min., except one case in which it continued for 32 min. due to the extreme bleeding and technical failure in anesthesia, and 3 cases in which ventricular fibrillation followed. As the occurrence of cardiac arrest depends also upon the dosage of prostigmine administered to the coronary arteries, it was impossible to investigate the relation between the period of circulatory interruption and the development of the cardiac arrest.

Atrial fibrillation:

Atrial fibrillation did not spontaneously develope before thoracotomy, but it was caused by the touch of the hand of surgeon and instrument on the

heart or by intracardiac manipulation. The duration of atrial fibrillation was not so long to cause disturbance in the circulation.

Ventricular extrasystole:

When ventricular extrasystole appeared very frequently, no differentiation between multiple ventricular extrasystole and ventricular tachycardia was possible.

Generally, these abnormal rhythms were caused by the inhalation of ether and were sometimes present before the cooling. In 2 cases of A.S.D., the additional inhalation of small amount of ether caused occurrence of ventricular rhythm at 35°C, and further cooling was given up. The short duration of these rhythms did not give so much influence on circulatory condition, but longer duration made us fear that ventricular fibrillation might follow spontaneously, and, as shown in Table II, occasionally we could not but give up the operation on the scheduled day or use N_2O anesthesia instead of ether. Since these arrhythmias were observed in all cases above 20 years of age, it may be considered that the damage of cardiac muscle is an important factor for the appearance of these arrhythmias in hypothermia under ether anesthesia.

Atrioventricular dissociation (A-V dissociation):

A-V dissociation was observed 15 instances in 13 cases. The appearance of this had no relation with the stage of the operative procedure and in some cases, it was already present before the establishment of the anesthesia. Usually it did not last for so long period to cause any serious change of the circulation, except in one case with large atrial septal defect, in which it lasted for about 130 min. after the suture of the defect, while heart action was controlled by pacemaker. In most cases of A-V dissociation observed in this series, ventricular frequency was not always less than atrial frequency, and this fact may be a cause of little influence of A-V dissociation on circulation.

Summary

As the consequence of the investigation of arrhythmia and disturbance of stimulus conduction, it may be concluded as follows.

(1) Although in some cases the operation had to be postponed and N_2O anesthesia had to be used instead of ether anesthesia, since ether inhalation might cause the fall of blood pressure and the appearance of ventricular extrasystole or ventricular rhythm, the electrocardiographic changes observed during this series of open heart surgery in hypothermia were reversible and disappeared in short time spontaneously or by the treatment.

(2) The fact that these changes were observed in serious cases above 20 years of age with severely damaged myocardium and marked abnomalities of hemodynamics, suggests that operation should be performed at as young as possible.

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Experimental Studies on Medionecrosis of the Aorta—Discussion on the Underlying Factors of Lathyrism, Ehlers-Danlos and Marfan's Syndromes

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Hiroshi OHTA, M.D., *and* Yoshiaki NODA, M.D.

Various causes of medionecrosis aortae idiopathica cystica have been postulated, but generally the primary factor is said to be the injury of vasa vasorum of the media. Both lathyrism and Marfan's syndrome show skeletal and vascular changes (medionecrosis of the aorta) and both are believed to arise from the abnormal metabolic changes of the mesoderm. Hyaluronidase which has hitherto been acknowledged as causative factor for the changes in the mesodermal ground substance has elicited similar changes in the bone and vessels in young rats as in Marfan's syndrome and lathyrism. In addition, vitamin E and chondroitin sulfate, known as an antagonist to hyaluronidase and protector of mesodermal changes, seemed to prevent excessive vascular and bone changes when used together with hyaluronidase. These results were then compared to those in lathyrism produced by aminoacetonitrile (A.A.N.: lathyrism factor).

We concluded that medionecrosis aortae cystica can also arise from the mesoderm metabolic disorder, and it was considered that Marfan's syndrome and lathyrism are similar pathological conditions and the basis lies in the abnormal disorder of the mesoderm.

MEDIONECROSIS aortae idiopathica cystica was first reported by Erdheim in 1929. It is a condition where the media of the aorta becomes necrotic showing broken elastic fibers and mucoid degeneration. Various causes of this condition have been postulated such as "endocrine substances," "endproducts of infection", "drugs", "congenital stenosis and malformation of the aorta", "pregnancy" and "hypertension", but the primary factor is said to be the injury of vasa vasorum of the media.

On the other hand, the study on lathyrism by Stockman and Ponseti[1),2)] has shown the development of spasms and sensory disturbances in the lower extremities in man after the ingestion of Lathyrus peas. In rats and mice similar symptoms together with bone changes of kyphoscoliosis and periosteal new bone formation and dissecting aneurysm can occur. The substance found in sweet peas was β-(-N-γ-L-glutamyl)-aminopropionitrile and from this aminopropionitrile was established as the causative factor. Later substances of similar chemical structure such as aminoacetonitrile (A.A.N.),

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bis-β-(cyanoethyl)-amine, methylamino-acetonitrile, β-mercaptoethylamine were found to be equally effective in bringing about these changes. These substances are known to cause mesodermal toxic effects[3] by inhibiting the formation or causing excessive destruction[4] of mesodermal chondroitin sulfate. The mechanism of the substances producing the disturbance, especially of the collagen in the mesodermal tissue metabolism has now become clear.

In connection with lathyrism, Marfan's syndrome presents an interesting comparison in its skeletal changes of arachnodactyly, kyphoscoliosis and cardiovascular changes of malformation and dissecting aneurysm. Both lathyrism and Marfan's syndrome show skeletal and vascular changes and both are believed to arise from the abnormal metabolic changes of the mesoderm.

The purpose of the present study is to see if hyaluronidase which causes the destruction of chondroitin sulfate and hyaluronic acid will also produce medionecrosis aortae and bone changes in young rats. In addition, vitamin E and chondroitin sulfate, known as an antagonist to hyaluronidase and protector of mesodermal changes, were also given together with hyaluronidase to compare the results. The results were then compared to that in lathyrism produced by A.A.N.

Methods

Twenty-three to 28-day-old rats were divided into 4 groups; group I received 400 units of hyaluronidase, group II, 400 units hyaluronidase plus 10 mg. of vitamin E, group III, 400 units hyaluronidase plus 4 mg. chondroitin sulfate, group IV, 5 mg. of A.A.N. subcutaneously daily and group V, 0.5 ml. of physiological saline was injected for the control purpose.

After 50 to 60 days, the rats were killed with chloroform or with a blow on the head. The animals were immediately dissected and the following procedures were taken. 1) Haematoxylin eosin, Elastica-Van Gieson's method and Elastica staining together with PAS and Lillie's Allochrome staining were made in sections from aortic root to the bifurcation in the abdomen. Electronmicroscope sections were also taken. 2) Vertebral, femoral, tibial and costal bone changes were also histologically examined. 3) The skin was similarly treated. In hyaluronidase and A.A.N. administered groups,[4] the changes in the eye were also histologically examined.

Results

Vascular Changes—

Histopathological findings:

i) Hyaluronidase group: Swelling and fragmentation of the elastic fibers were seen with Elastica and Elastica-Van Gieson's method (Fig. 1). Edema of the media was seen in haematoxylin eosin staining. In part with Lillie's Allochrome staining, edema of the media and diffuse appearance of Schiff's positive substance were seen and presented a picture of changes in the

ground substance. Medionecrosis aortae idiopathica cystica-like cyst was seen in this section (Fig. 2). In general, the affinity for stains of the elastic fibers was lowered. In some sections, the elastic fibers did not show any staining.

ii) Hyaluronidase plus vitamin E group: In most of the animals, no abnormal findings were present. In a few cases, however, swelling, fragmentation and deterioration of staining ability of the elastic fibers were seen. Of these cases, as shown in Fig. 3, elastolysis-like findings were seen but other parts were nearly normal. Generally it can be said that the tissue changes are remarkably few in contrast to those in the hyaluronidase group.

iii) Hyaluronidase plus chondroitin sulfate group: Although edema of the media and swelling of the elastic fibers are seen, the tissue changes are fewer when compared to group ii). Generally the staining ability was lowered (Fig. 4).

iv) A.A.N. group: Generally, the changes in the media are not so marked as those in hyaluronidase group but the deterioration of the staining ability, swelling, fragmentation of the elastic fibers and edema of the muscle fibers were present. In part, as shown in Fig. 5, cysts were observed possessing PAS positive mucoid like substances.

v) Physiological saline group: No changes were seen.

Table I shows the vascular changes of the cases mentioned above.

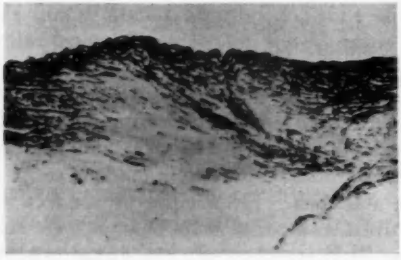

Fig. 1.

Fig. 2.

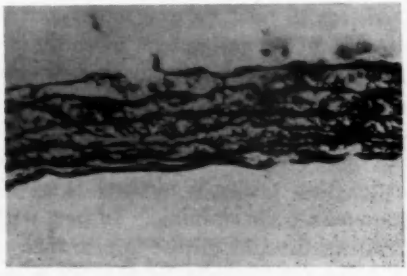

Fig. 3.

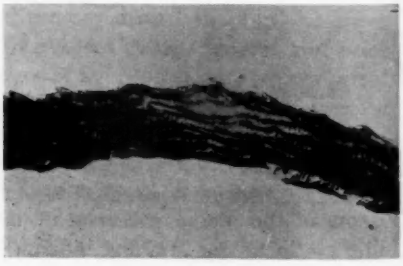

Fig. 4.

Fig. 5.

Table I.

			Control	Hyaluronidase	Hyaluronidase +Vit. E	Hyaluronidase +Chond. sulf.	A.A.N.
Cases			10	15	10	10	15
Experimental methods			Physiological Saline 0.5 c.c./day ×50 days	Hyaluronidase 400U/day ×50 days	Hyaluronidase 400U+Vit. E 10 mg/day ×50 days	Hyaluronidase 400U+Chond. sulf. 4 mg/day ×50 days	A.A.N. 5 mg/day ×50 days.
Histological findings	Media	Thickening of intima	−	−	−	−	−
		Elastic fibers: Deterioration of staining	±	##	+	+	+
		Elastic fibers: Swelling	±	##	+	+	+
		Elastic fibers: Fragmentation	−	##~###	±	±	+
		Edema and degeneration of muscle fibers	+	##~###	+	+	+
		Cyst	−	+	−	−	+
		Schiff's positive substance	−	##	±	±	+
		Aneurysm-like dilatation	−	−	−	−	−
	Adventitia	Changes of vasa vasorum	−	−	−	−	−
		Thickening	−	−	−	−	−

Electron-microscopic findings:

Exactly similar changes as seen in histopathologic picture were obtained.

Bone Changes—

Similar changes were seen in tibia, femur and costal bones. A representa-

tive tibial epiphyseal cartilage change is shown.

In normal epiphyseal cartilage, as shown in Fig. 6 and Fig. 7, is divided into 1) thin germinal layer, 2) proliferating zone, 3)–a zone with growth of cells and intercellular substance, –b zone of intracellular edema, and 4) zone of calcification.

i) Hyaluronidase group: As shown in Fig. 8 and Fig. 9, the second zone is extremely elongated and the cartilage substance is deeply stained. In the third zone, the so-called intracellular edema is slight but a marked difference is seen in the fourth zone. The attachment of bony substance to the cartilage columns is poor and bony trabeculae is fine and widely separated simulating the condition of osteogenesis imperfecta. Furthermore,

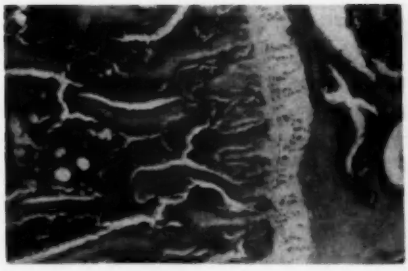

Fig. 6.

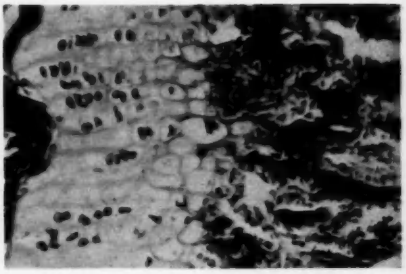

Fig. 7.

Fig. 8.

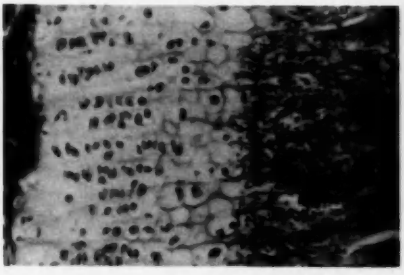

Fig. 9.

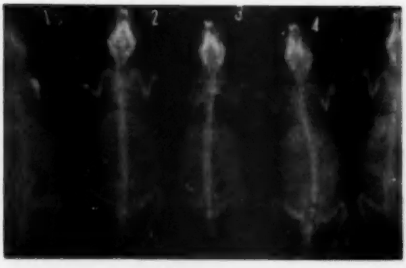

Fig. 10.

Fig. 11.

in the hyaluronidase group, the vertebral picture showed extreme kyphoscoliosis in some cases as in Fig. 10.

ii) Hyaluronidase plus vitamine E group: The second zone is elongated but is almost normal. The third zone is also somewhat extended. The fourth zone is essentially normal and the width of the bony trabeculae is increased as compared with that of the hyaluronidase group (Fig. 11).

iii) Hyaluronidase plus chondroitin sulfate group: The width of the second zone is nearly normal and the cellular formation is dense. In this portion, the staining is greater in the cartilage substance than that of those cases in which hyaluronidase was used alone. The third zone is somewhat wider and the fourth zone seems to show a better bony trabeculae formation (Fig. 12).

iv) A.A.N. group: As shown in Fig. 13, an almost normal picture is seen but a deeper staining is present in the cartilage substance in the first and second zone. The fourth zone is practically normal. In one case of A.A.N. group, as shown in Fig. 14, a fracture of the thoracic vertebrae was observed.

The bone changes are summarized in Fig. 15.

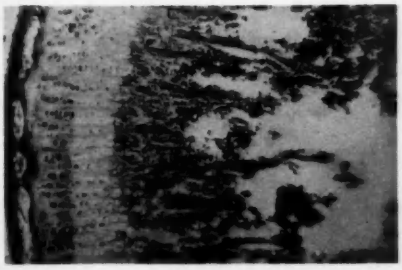

Fig. 12.

Fig. 13.

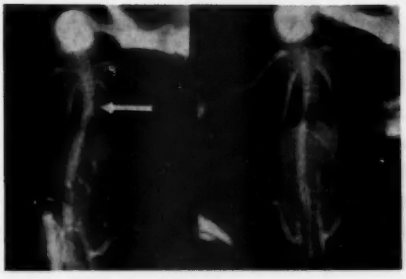

Fig. 14.

Skin Changes—

Both hyaluronidase and A.A.N. groups seemingly presented thin, extremely relaxed and elastic skin on palpation and no marked changes were observed histologically.

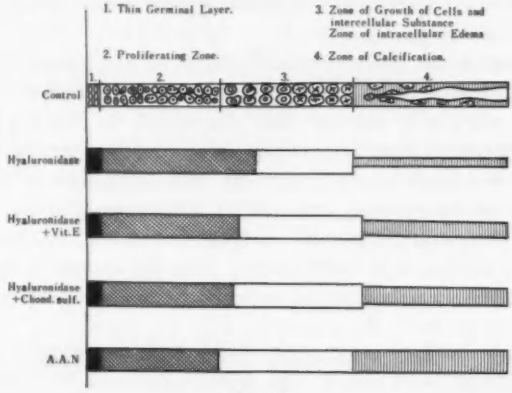

Fig. 15.

Ocular Changes—

In hyaluronidase and A.A.N. groups, no particular changes were evident ophthalmologically and histologically.

E.C.G. Changes—

No abnormalities were seen.

Discussion

Marfan's syndrome was first reported under the name of dolichostenomelia by Marfan in 1896. There have been many views on the cause of this syndrome but in general, it is conceded that this disease arises from the abnormal metabolism or abnormal growth of the mesoderm tissue.

In lathyrism, the changes appear in the mesodermal ground substance[5] which contains the mucopolysaccharide, chondroitin sulfate and hyaluronic acid. Dasler[6] states that lathyrism is due to the disturbance of the collagen metabolism.

Hyaluronic acid is widely distributed in aqueous humor, vitreous body, navel cord, joint fluid, skin, intima, media and heart valves. It is an acid mucopolysaccharide and is present in intercellular spaces of the connective and supportive tissues. Hyaluronidase hydrolyses this polysaccharide and forms a low molecular sugar derivative. Chondroitin sulfate, on the other hand, is one of the chief substance of the cartilage and performs the role of cementing the cartilage. It is also present in the navel cord and the connective tissues. Chondroitin sulfate is divided into A, B and C by its reaction to the type of hyaluronidase. Those acted on by testicular hyaluronidase and present in the cartilage is chondroitin A, and according to Meyer,[7] the approximately 1% of acid mucopolysoccharide present in dry weight of aorta, 1/3 is chondroitin sulfate A and 1/7 is hyaluronic acid. Therefore, it can be compre-

hended that in mesoderm type diseases the aorta and bone changes can appear as an entity.

In vascular changes, the changes in the media can be seen in Marfan's syndrome and lathyrism. In young rats of our present study, hyaluronidase and A.A.N. administered cases showed similar changes in the media which consisted of swelling and fragmentation of the elastic fibers and cyst formation presenting a medionecrosis aortae idiopathica cystica-like picture. Moreover, the hyaluronidase group showed a stronger changes than A.A.N. group. The changes of medionecrotic cysts were located near the base of the aorta and is believed to be due to the stress and the metabolic changes which are apt to occur in that region.[8]

Boyd[9] states that the bone changes in Marfan's syndrome is characterized by the picture of osteogenesis imperfecta and Albanese mentions a state of hyperchondroplasia, while Sweet[10] attributes pectus excavatum to excess growth of the ribs. Meanwhile, in our hyaluronidase group, both osteogenesis imperfecta and vascular changes present Marfan's syndrome.

However, in the A.A.N. group, only slight vascular changes were observed and histological changes in the bone were almost non-existent, though there was a fracture of the thoracic vertebrae in one case. Literatures[11), 12)] indicate that with A.A.N. widening and irregular production are observed in the epiphyseal cartilage and these conditions are similar to those produced by hyaluronidase.

The fact that hyaluronidase which has hitherto been acknowledged as causative factor for the changes in the mesoderm has elicited similar changes in the bone and vessels in young rats as in Marfan's syndrome and lathyrism shows that these two clinical conditions are very similar in nature of their origin and clearly indicates a state of mesoderm abnormality in growth and metabolism.

Contrary to our expectations, hyaluronidase and A.A.N. effects on the skin of young rats were not very evident and Ehlers-Danlos syndrome-like changes in the skin such as irregularity, degeneration and reduction of the collagen fibers together with increase and irregularity of elastic fibers were not seen.

Clinical cases have been reported where Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta,[13] congenital heart disease,[14), 15)] chest deformity[13] and dissecting aneurysm were present together.

Shaper has differentiated Marfan's syndrome from Ehlers-Danlos syndrome by expressing the former as " Dystrophia mesodermalis congenita mit vorwiegend ligamentär-ossarem Syndrom " and the latter as " Dystrophia mesodermalis congenita mit vorwiegend cutan-ligamentärem Syndrom " but believed similar etiological basis of these 2 conditions.

Tissue changes were less in groups where vitamin E and chondroitin sulfate were used together with hyaluronidase than with groups where hyaluronidase was used alone. Lee[16] has reported that vitamin E can prevent lathyrism. Furthermore, Dasler[17] reported that the administration of gelatin,

the source of hydroxyproline, would retard the development of lathyrism. Recently Sjoerdsma[18] reported that hydroxyproline was increased in urine in Marfan's syndrome suggesting a similar biochemical condition between lathyrism and Marfan's syndrome. McKusick also emphasized that Marfan's syndrome is a condition of biochemical defect of the connective tissue because of its similarity to lathyrism. It is of interest that he considers Marfan's and Ehlers-Danlos syndromes as hereditary congenital connective tissue diseases.[19]

In Hurler's syndrome which McKusick mentions as a hereditary connective tissue disease, Meyer[20] reported that chondroitin sulfate B, heparitin sulfate and other mucopolysaccharide are abnormally excreted in the urine pointing to the connective tissue metabolic disorder and suggested the possibility of future study. In any rate, since no effective form of treatment is available at the present time it is believed that further study from the standpoint of normally existing hyaluronic acid and chondroitin sulfate is desireable.

Summary

Hyaluronidase, A.A.N. (lathyrism factor), vitamin E, and chondroitin sulfate were given to weanling rats alone and in combinations, then vascular, bone, skin and ocular changes were studied morphologically.

(1) Vascular chages in the media, elastic fiber swelling, fragmentation and cyst formation (Medionecrosis aortae cystica) were more pronounced in hyaluronidase administered rats than those of A.A.N.

Hyaluronidase caused bone changes of osteogenesis imperfecta similar to Marfan's syndrome and kyphoscoliosis was also produced. In A.A.N. group, pronounced bone changes were not seen with exception of a case of fractured thoracic vertebrae.

(2) Medionecrosis aortae cystica can also arise from the mesoderm metabolic disorder.

(3) Marfan's syndrome and lathyrism are similar pathological conditions and the basis lies in the abnormal disorder of the mesoderm.

(4) Vitamin E and chondroitin sulfate seemed to prevent excessive vascular and bone changes when used together with hyaluronidase.

(5) No changes in the skin suggesting Ehlers-Danlos syndrome were noted after the use of hyaluronidase and A.A.N. though the skin became softer and thinner.

(6) The use of hyaluronidase and A.A.N. did not produce any eye or E.C.G. changes.

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Study on the Ventricular Activation of the Heart of Cattle and Goat

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and Hideo UEDA, M.D.*

In cattle and goat, the mode of ventricular activation was persued by the multiple chest leads, esophageal leads, direct epicardial leads and intracardiac leads in both right and left heart. The area showing QS pattern was invariably found on direct epicardial leads, and the tracings from both ventricles showed several different patterns such as QS, rS and RS. In the tracings of the part cephalad from atrioventricular groove, qR pattern was revealed. From these findings, the ventricular activation is considered to be directed toward apicobasal as well as endocardial-epicardial. This assumption is consistent with the recent knowledges on the special distribution of the Purkinje fibers in ungulates.

IT has been pointed out by some authors that the electrocardiogram of ungulates show some peculiar patterns in extremity leads as well as in precordial leads.[1),2)] The QRS complexes are fairly similar among cattle, horse, goat, sheep and camel, and are distinctly different from those of man and dog though the cause of the difference has not been conclusively studied by analytical methods.

Kisch,[1)] in 1948, observed upright QRS complex by intraventricular leads and downward QRS complex in direct epicardial leads in calves, and concluded that the direction of ventricular excitation was from the epicardium toward the endocardium, which was quite opposite to that of normal man and dog, but was somewhat alike to the mode of ventricular excitation in WPW syndrome.[4)]

The purposes of this paper are to clarify whether Kisch's opinion is valid or not in adult cattle and goat, and to analyse the genesis of the peculiar electrocardiographic patterns of ungulates.

Materials and Method

Nine cattles and 12 goats were used in this experimental study. The age, sex and body weight are tabulated in Table I. Multiple chest leads, intracardiac leads, esophageal leads, and direct epicardial leads were taken, using an ink-writing, one-channel electrocardiograph.

1. Chest leads. Multiple chest leads were recorded in a lateral recumbent

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Table I. The Experimental Animals and the Kinds of the Special Leads Used

	No.	Age	Sex	Body weight (Kg.)	Leads
Cattle	1	3	M	230	R.L.
	2	3	M	265	C.R.L.D.
	3	7	F	450	R.
	4	6	F	380	R.
	5	30 days	M	40	C.E.R.
	6	30 days	M	30	C.E.R.
	7	4	F	430	C.R.L.D.
	8	3	M	333	R.L.E.D.
	9	4	F	450	C.E.L.D.
Goat	1	5 Mon.	M	12.0	C.E.R.L.D.
	2	5 Mon.	M	12.6	C.E.R.
	3	5 Mon.	M	11.1	C.E.R.L.D.
	4	3	F	32.0	C.R.L.D.
	5	3	F	33.0	C.
	6	3	F	38.0	C.E.R.L.D.
	7	4	F	40.0	C.E.R.L.D.
	8	3	M	35.0	L.
	9	2	M	26.5	R.L.
	10	2	M	28.8	R.
	11	2	F	11.8	R.
	12	3	F	28.6	C.R.L.D.

M: male, F: female.
C: chest lead, D: direct epicardial lead, E: esophageal lead,
L: left intracardiac lead, R: right intracardiac lead.

position in most instances and in standing position in rare cases, without anesthesia. Fig. 1 shows the positions of the reference electrode, and the lines A, B, C, D and E represent the circumferential lines on the body surface, cut by perpendicular planes. The anal region was selected as a point for an indifferent electrode.

2. Esophageal leads. Recording was made at every 1–5 cm. interval successively by pulling out the electrode which had been inserted in the stomach.

3. Intracardiac leads. Right and left heart catheterization were performed through left jugular vein and through carotid artery respectively in a lateral recumbent position under local anesthesia, when needed.

Though catheterization was not always carried out under the control of fluoroscopy because of a thick trunk of the animals, it could be differentiated mainly by the E.C.G. patterns of intracardiac leads whether the tip of the catheter was actually within the ventricle or not, as discussed later.

4. Direct epicardial leads. Chest was opened under local anesthesia and artificial respiration when needed, and recordings from epicardium were made. The anal region was selected for the site of indifferent electrode in all cases.

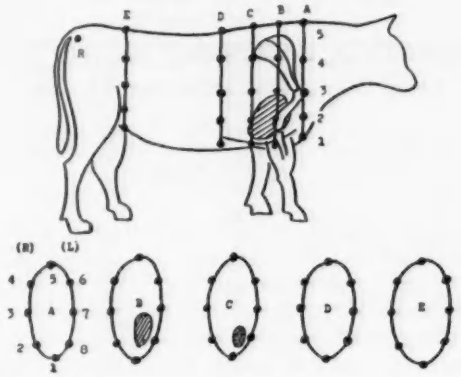

Fig. 1, A. Exploring points of multiple chest leads in cattle.

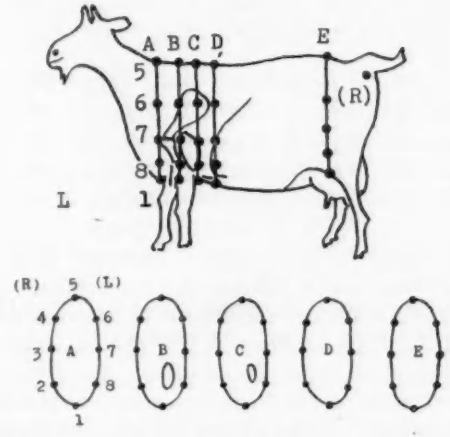

Fig. 1, B. Exploring points of multiple chest leads in goat.

Results

1. Ventricular complexes in chest leads

All cases of cattle and goats, with one exception of goat, showed a quite similar pattern of ventricular complex in the chest leads, typical cases of which were represented in Fig. 2.

The remarkable findings on the ventricular complexes are the following:

(1) Every explored point on the neck, shoulder and back of the forward half of the trunk revealed qR or R pattern.

(2) Relatively circumscribed region adjacent to the heart apex showed QS or rS pattern.

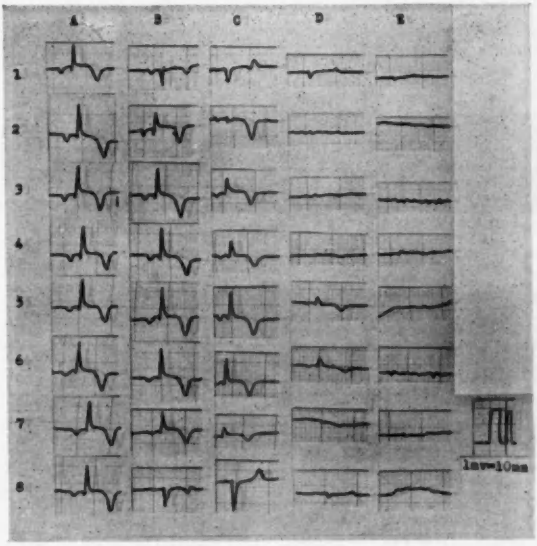

Fig. 2, A. Ventricular complexes in chest leads in cattle.

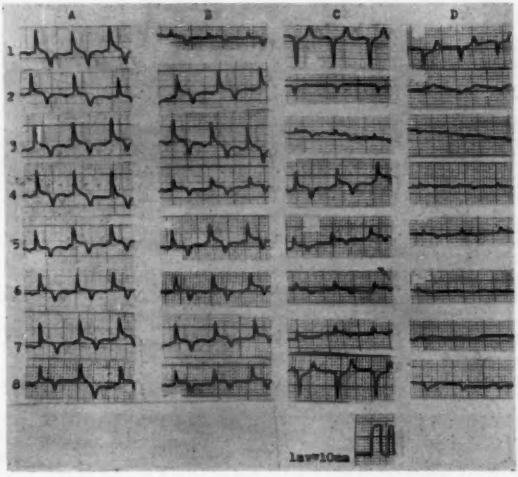

Fig. 2, B. Ventricular complexes in chest leads in goat.

(3) The ventricular complex recorded in the leads from the reference points along the lines D and E usually showed low voltage QRS complex.

One exceptional case (Goat No.6) showed rS or QS pattern of ventricular complex in the leads from the backward points on A and B lines.

2. Ventricular complexes in epicardial direct leads

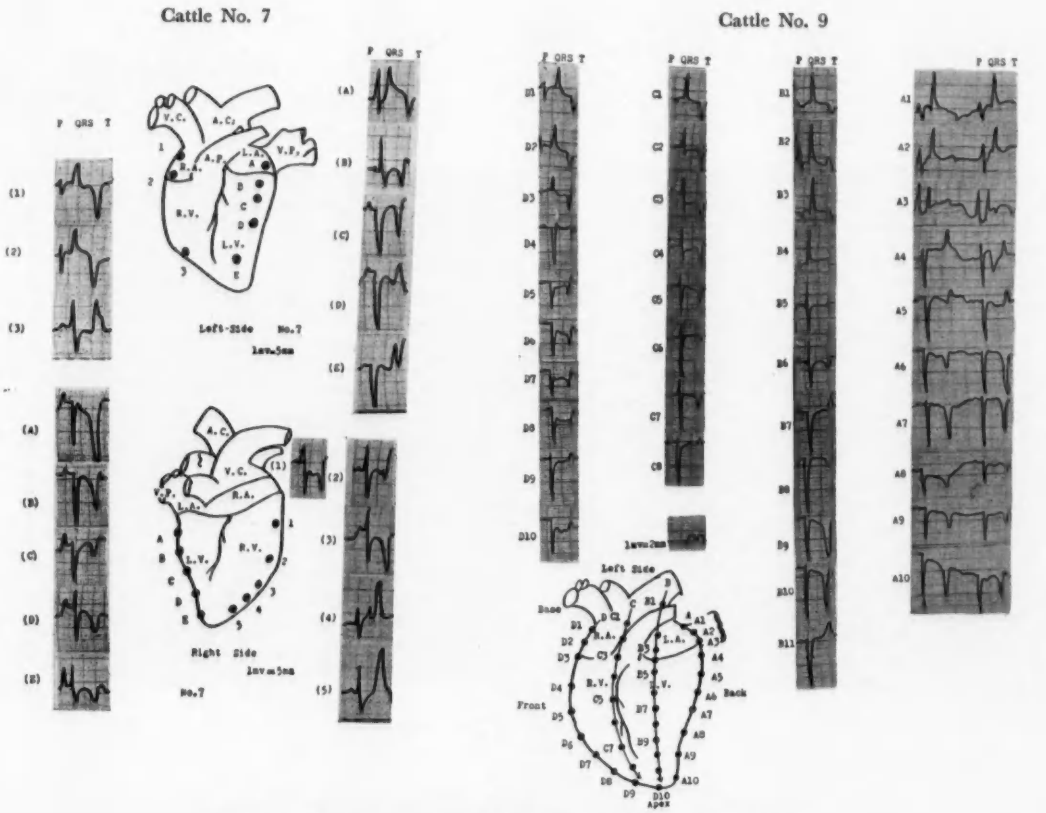

Fig. 3, A. Ventricular complexes in epicardial direct leads in cattle.

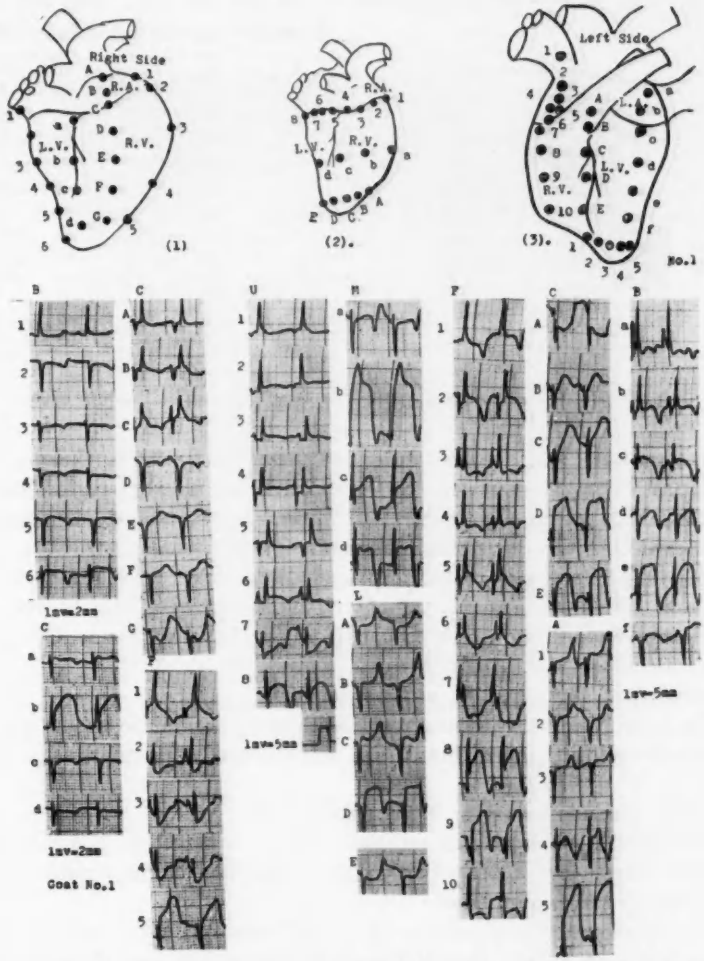

Fig. 3, B. Ventricular complexes in epicardial direct leads in goat.

Tracings obtained from the surface of atria or great vessels cephalad from the atrioventricular groove, showed qR or R pattern invariably. From the ventricular surface in the majority of instances, qR or R pattern was restricted on the basal, relatively small area of both ventricular surfaces. On the other parts RS, rS and QS patterns were revealed, and the distribution of ventricular surface exhibiting each pattern was puzzlingly intermingled, and the width for each pattern was unexpectedly different in each case.

The most remarkable finding was QS pattern at the apex in many cases which should be R or RS in man and dog (Fig. 3).

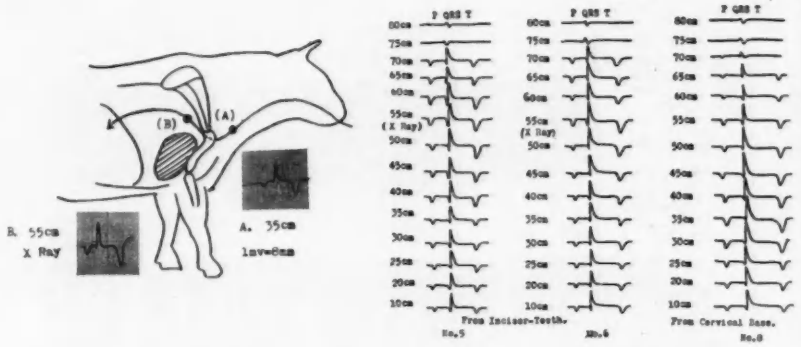

Fig. 4. Esophageal leads and ventricular complexes in these leads in cattle.

In some cases, the area revealing QS pattern extended further to antero-lateral part of both ventricles. In other cases, an isolated region on right ventricle also showed QS pattern. In some cases, almost all ventricular surface exhibited QS or rS pattern except for the basal part.

In 5 experiments in goat, diaphragmatic semidirect leads were taken to explore the postero-apical region of the heart. On the region which showed marked pulsation due to cardiac beat, in all 5 cases, QS pattern was revealed.

3. Ventricular complexes in esophageal leads

The configuration of ventricular electrogram was quite similar on every esophageal exploring point, that is, qR in both cattle and goat, as illustrated in Fig. 4.

4. Ventricular complexes in intracardiac leads

Though the position of the catheter tip was confirmed by X-ray or autopsy in some cases, it was presumed by the features of electrographic patterns in majority of the experiments.

The electrographic criteria for the actual exist of the catheter tip within the ventricle were: (1) Small P-wave in magnitude and showing neither intrisic deflection nor predominantly negative deflection, (2) RS-T segment elevation caused by the catheter tip against the ventricular endocardium.

By these criteria, the possibility of catheter tip being in the atrial cavity, in the great vessels cephalad from atrioventricular groove, or in the circumflex branch of coronary vessels could be excluded though the possibility of the catheter tip being in inferior vena cava or pulmonary artery could not be ruled out completely. A set of serial electrograms was recorded by withdrawing the catheter from the point which seemed to be in ventricular cavity by the above criteria to the point showing intraatrial or juxtaatrial pattern, which had large and peaked or diphasic P-wave.

In the both right and left intraventricular leads, several patterns, such as RS, rS and QS, were obtained.

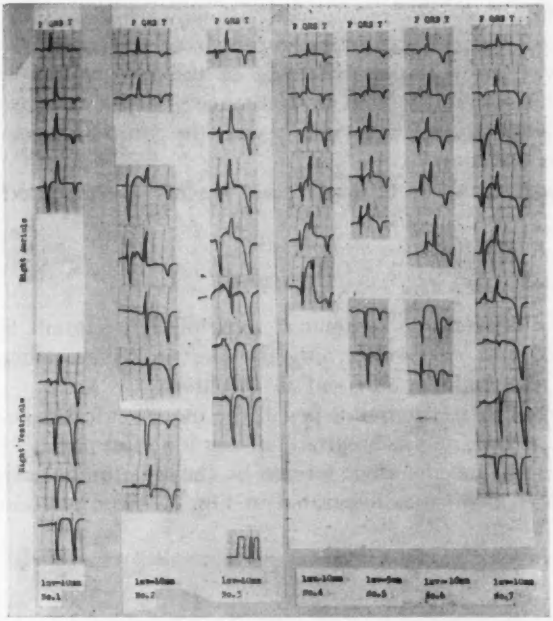

Fig. 5, A. Intracardiac tracings by right heart catheterization in cattle.

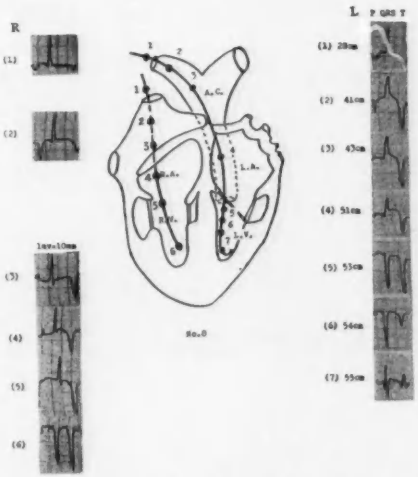

Fig. 5, B. Intracardiac tracings by right and left heart catheterization in cattle No. 8.

It was impressive that QS pattern was obtained in deeper level near the cardiac apex, and RS pattern in the higher level near the base, though the exact positional correspondence could not be confirmed. At any rate, it was to be noted that the predominantly downward deflection was observed and no R or qR pattern was present in apparently intraventricular tracings.

There was no essential difference in the tracing from right and left ventricle in this study to suggest the existence of asynchronism of the activation of both sides of the ventricular septum in cattle and goat as normally found in man and dog.[6]

The typical examples of intracardiac tracings were reproduced in Figg. 5 and 6.

Discussion

It may be desirable to summarize some of the anatomic features of the heart of cattle and goat concerning the electrical phenomenon before the discussion on the findings observed in this study.

The heart of these ruminants lies in the more ventral part of the thorax than in man and dog, and its longitudinal axis is almost parallel to the sagittal plane of the trunk, and the angle formed by the longitudinal axis of the heart and the trunk is likewise as illustrated in Fig. 7. The position of the heart

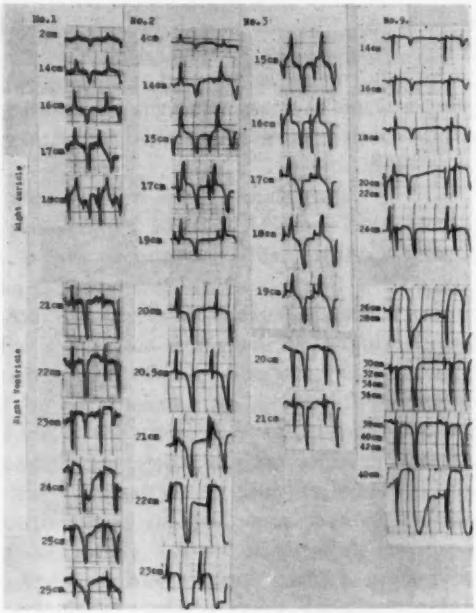

Fig. 6, A. Intracardiac tracings by right heart catheterization in goat.

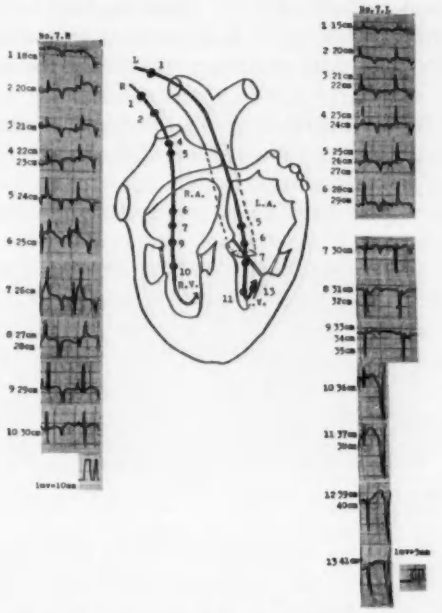

Fig. 6, B. Intracardiac tracings by right and left heart catheterization in goat No. 7.

to the sagittal plane shifts somewhat toward the left as a whole. Both right atrium and ventricle occupy the ventro-cranial part of the heart, and the left atrium and ventricle occupy dorso-caudal part.

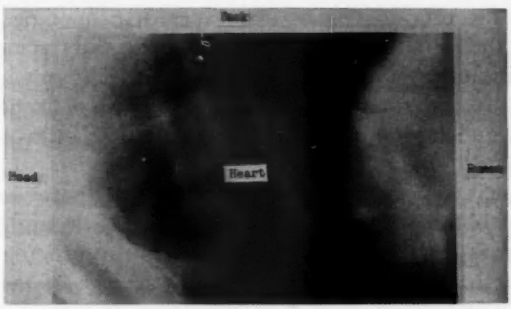

Fig. 7. The position of the heart of cattle in the thorax, illustrated by X-ray. Lateral view.

Difference in the thickness of right and left ventricular wall is essentially the same as in dogs.

The esophagus passes above the basal part of the heart throughout its

course, and does not contact with the posterior wall of the heart.

There is no gross difference in the macroscopic composition of the heart itself among cattle, goat, dog, and man, except for the positional specificity in the thorax.

As described in the introduction of this paper, it has been noted that the electrocardiogram of some kinds of ungulates is apparently different from that of man or dog in conventional leads. Some of the peculiar patterns are reproduced in Fig. 8. It has been a problem to be solved that how much

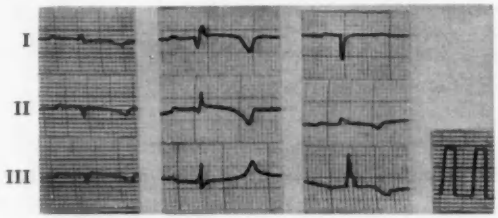

Fig. 8. Several patterns of the limb leads on cattle.

these patterns are due to the positional specificity of the heart of the animals, or due to the mode of ventricular excitation specific for these animals. Ueda, one of the authors, and associates[5] have studied this problem in horse by multiple precordial leads, and suspected that the ventricular excitation is directed apico-basal as well as endocardial-epicardial. Kisch,[3] applying the technique of cardiac catheterization and multiple direct epicardial leads to this problem on young calves, has concluded that ventricular excitation of the animal was rather directed toward epicardial-endocardial, contrarily to that of normal man and dog. Though his speculation is very attractive as described in the introduction of this paper, it cannot persuade us completely because the signification of the intraventricular tracings obtained by his method seems to be unsettled to the authors. His conclusion has been derived from the facts that the predominantly negative deflection in the direct epicardial leads and largely upright deflection in the intraventricular leads have been obtained.

In the present experiment on cattle and goat, however, QS, rS and RS patterns were obtained both in left and right ventricle, and predominantly upright QRS was not seen in apparently intraventricular leads. This discrepancy may be due to the difference in the age of the experimental animals, but close examination of the reproduced tracings of Kisch's paper discloses that rS pattern has also been obtained in the intraventricular leads, and some of his records of " intraventricular leads " may be considered to show that the catheter tip was outside of the ventricular cavity judging from the shape of the P-wave.

The authors' findings on direct epicardial leads are essentially consistent

with those of Kisch. Though there are some differences in each case, QS or rS pattern is recorded on more or less wide area of the ventricular surface. The area in which these peculiar patterns are recorded, in most cases of this experiment, occupies the apical region, and in some cases it extends to more basal, lateral or posterior in the left ventricle, and further anterobasal or posteroapical portion in the right ventricle, isolated or continuous to the area of left ventricle.

The fact that the QS pattern can be recorded on the normal epicardium of cattle and goat, is consistent with the recently ascertained anatomical and physiological knowledges. Ter Berg[7] and Meyling[8] have found that the Purkinje fibers in some species of ruminants form a network not only in the septum but also throughout the whole parietal wall of both ventricles. From these findings, it may be possible that the transmural excitation is almost synchronous. This deduction has been verified in the study of Durrer and associates[9] on sheep by the technique of multiple intramural electrodes.

Furthermore, Ter Berg and Meyling have found that the density of the network of Purkinje fibers diminishes in the basal region of the ventricular wall and the septum, and that the fibers at the basal part of the septum do not originate from the main bundle, but from points situated in more apical portion. From these findings, it is expected that activation of the basal part of ventricle, as a whole, is later than that of the apical part. In this experiment, ventricular complex showing R or qR pattern is recorded in the direct epicardial leads at the basal part of ventricle near-by atrioventricular groove, in the direct atrial epicardial leads, in the intraatrial leads, and intravascular leads cephalad from atrioventricular groove.

Ventricular complex in the intraventricular leads, on the other hand, shows QS, rS and RS patterns. The positions in the ventricular cavity from which these 3 patterns are recorded tend to be arranged successively in an apicobasal direction, though it is not exactly confirmed.

It may be postulated that the activation of the ventricle, in cattle and goat, is conducted in an apicobasal as well as transmural direction as a whole, though much more complexed activation must be considered in the more precise discussion according to puzzling distribution of various patterns on epicardial surface.

From these considerations on the mode of ventricular activation and the anatomical position of the heart relative to the trunk, it is considerably easy to understand the cause of QS or rS pattern in precordial part of the chest, qR pattern in esophageal leads and in the leads taken from the craniodorsal parts of the trunk, and further the apparently peculiar patterns in limb leads of these animals.

It is concluded that the ventricular activation in the heart of ungulates is quite different from that in man or dog because of the difference in the distribution of the Purkinje net work. However this discrepancy may be due to rather slight difference in the distribution of Purkinje fibers in the parietal

wall, because some recent studies[9)-11)] by intramural leads have suggested that the deeper penetration of Purkinje fibers into the ventricular wall in dogs than hitherto assumed.

Summary

(1) Multiple chest, esophageal, intracardiac leads and direct epicardial leads were taken in cattle and goats to study the mode of ventricular activation of ungulates.

(2) There was little difference between cattle and goat in these special leads.

(3) In direct epicardial leads the area showing QS pattern was invariably observed, and in the intraventricular tracings, QS, rS and RS patterns were noted.

(4) From the findings in direct epicardial leads and intraventricular leads, it was assumed that the ventricular activation, as a whole, was directed from apex to base, though transmural activation might play a role at least in some regions of ventricular wall. This assumption could explain well the findings of multiple chest leads and esophageal leads.

Addendum

This study was reported in divided parts before the proceedings of the 47th (April, 1959) and the 49th (April, 1960) Meeting of the Japanese Society of Veterinary Science, and the 13th Meeting of Kanto Branch of the Japanese Circulation Society (May, 1959). Publications in Japanese are in Jap. Circulation J. 23: 1193, 1959,[12)] and Journal of Faculty of Agriculture Iwate University 4:4, 1960.[13)]

While this paper was in press our attention was called to the studies by R.L. Hamlin, C. R. Smith and R. W. Redding,[14)15)] closely related to the present study. Our conclusions agree in general with theirs.

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Algebraic Reflections on the Vector Concept in Electrocardiography

Part II. Structure of the Electric Field

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In the previous report, the definition of vector was reconsidered and the method to construct the electric field on the body surface was discussed. The present paper is concerned with the analysis of the structure of the field. Here, a method to decompose the filed to the sum of fields of lower degree (Chapter 3), and an "*isomorphic image*" of the field is demonstrated so as to make its intuitive understanding possible (Chapter 4). The meaning of the expression *ELECTROCARDIOCRAM IS SCALAR*, which is seemingly inconsistent with the previous statement *ELECTROCARDIOGRAM IS VECTOR*, is explained. As an application of the results in these 2 chapters, the theoretical limitation of the vectorcardiography is discussed quantitatively.

AS was mentioned before,[19] the purpose of this study was to find a new principle in the conventional vector theories and to exclude semi-abstract concepts and unnecessary assumptions. The definition of the vector was reconsidered and the method to construct the electric field on the body surface was demonstrated in Part I[19] and here, the structure of the field will be analysed algebraically and geometrically.

Chapter 3.

Decomposition of the Electric Field

At the beginning, the fundamentals for the finite-dimensional vector space will be discussed.

All the ideals of $\mathfrak{A}$ form a complementary modular lattice,[1),3)] when a law of composition $A_1 \cap A_2$ of ideals A_1 and A_2 and the other law of composition $A_1 \cup A_2$ are defined respectively as their intersection and direct sum $A_1 + A_2$.

The set $\{A\}$ of k-ideals $A_1, A_2, \ldots\ldots, A_k$ of $\mathfrak{A}$ is named as a "*series of ideals*", and a subset of $\{A\}$ is a "*subseries*" of $\{A\}$. Dimension-number of an ideal A is shown by symbol $dA (dA \geqq 0)$. The least upper bound of $\{A\}$ is $\boldsymbol{A}_k = A_1 \cup A_2 \cup \ldots\ldots \cup A_k$. $d\boldsymbol{A}_k \leqq dA_1 + dA_2 + \ldots\ldots + dA_k$ When $d\boldsymbol{A}_k = \sum_{i=1}^{k} dA_i$ holds, $\{A\}$ is said "*independent*". Then the followings are valid.

1) A subseries of $\{A\}$ is independent.

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2) $A_i \cap A_j = 0 \quad A_i, A_j \in \{A\} \quad , \quad i \neq j$

3) $A_i \cap \boldsymbol{A}'_i = 0 \quad (\boldsymbol{A}'_i = A_1 \cup A_2 \cup \cdots\cdots \cup A_{i-1} \cup A_{i+1} \cup \cdots\cdots \cup A_k)$ And conversely, if this relation holds for any i, $\{A\}$ is independent.

4) When an element of A_i is α_i, $\sum_{i=1}^{k} \alpha_i = 0$ holds only in the case when $\alpha_i = 0 \quad (i = 1, 2, \cdots\cdots, k)$.

Here, the outline of proofs for 3) and for 4) will be demonstrated.

$$d\boldsymbol{A}_k = d(\boldsymbol{A}_{k-1} \cup A_k) = d\boldsymbol{A}_{k-1} + dA_k - d(\boldsymbol{A}_{k-1} \cap A_k) \quad [1]$$

In the same manner, the following holds for any h $(h = 0, 1, 2, \cdots\cdots, k-1)$.

$$d\boldsymbol{A}_{k-h} = d\boldsymbol{A}_{k-h-1} + dA_{k-h} - d(\boldsymbol{A}_{k-h-1} \cap A_{k-h})$$

By integrating this formula for all h,

$$d\boldsymbol{A}_k = \sum_{i=1}^{k} dA_i - \sum_{j=1}^{k-1} d(\boldsymbol{A}_j \cap A_{j+1})$$

As $\{A\}$ is independent, $\sum_{j=1}^{k-1} d(\boldsymbol{A}_j \cap A_{j+1}) = 0$ Then, $d(\boldsymbol{A}_j \cap A_{j+1}) = 0$

Hence, we get the relations such as $A_1 \cap A_2 = 0$, $(A_1 \cup A_2) \cap A_3 = 0$, $(A_1 \cup A_2 \cup A_3) \cap A_4 = 0, \cdots\cdots$, $(A_1 \cup A_2 \cup \cdots\cdots \cup A_{k-1}) \cap A_k = 0$ Furthermore, the order among the elements in $\{A\}$ is not determined, and any ideal in $\{A\}$ may be appointed as A_k. So 3) holds evidently. The converse may also be proved easily.

Next, 4) will be proved.

$$\alpha' + \alpha_k = 0 \quad (\alpha' = \alpha_1 + \alpha_2 + \cdots\cdots + \alpha_{k-1} \quad , \quad \alpha' \in \boldsymbol{A}'_k)$$

If $\alpha_k \neq 0$, then $\alpha' = -\alpha_k \neq 0$ and $-\alpha_k \in A_k$, therefore, $\alpha' \in A_k \cap \boldsymbol{A}'_k$ This result is inconsistent with the character 3). Hence, $\alpha_k = 0$ Just in the similar way, it is proved that $a_i = 0$ holds for any i.

When $\{A\}$ is independent and the relation $\boldsymbol{A}_k = \mathfrak{A}$ holds, we say that A_i $(i = 1, 2, \cdots\cdots, k)$ in $\{A\}$ is a "*component of* $\mathfrak{A}$", and that "$\mathfrak{A}$ *is decomposed to k-components* $A_1, A_2, \cdots\cdots, A_k$".

$$d\mathfrak{A} = n = \sum_{i=1}^{k} dA_i \qquad (3\text{–}3)$$

Now the method will be demonstrated here, how to decompose $\mathfrak{A}$ to its components $A_1, A_2, \cdots\cdots, A_k$, so as to comply with given conditions $dA_i = n_i$, $\sum n_i = n$ $(i = 1, 2, \cdots\cdots, k)$.

First of all, a n_1-dimensional ideal A_1 is arbitrarily selected $(dA_1 = n_1)$. As $\mathfrak{A}$ is the complementary modular lattice, A'_1 is determined though not uniquely, and $\mathfrak{A} = A_1 \cup A'_1$, $dA'_1 = n - n_1$ hold. Next, a n_2-dimensional ideal is arbitrarily, selected $(dA_2 = n_2)$. Then, A'_2 is determined and $A'_1 = A_2 \cup A'_2$, $dA'_2 = n - n_1 - n_2$ $\therefore$ $\mathfrak{A} = A_1 \cup A_2 \cup A'_2$

Further, a n_3-dimensional A_3 is selected $(dA_3 = n_3)$. $A'_2 = A_3 \cup A'_3$, $dA'_3 = n - n_1 - n_2 - n_3$ $\therefore$ $\mathfrak{A} = A_1 \cup A_2 \cup A_3 \cup A'_3$ By repeated application of these operations, $\mathfrak{A}$ is evidently decomposed as

$$\mathfrak{A} = A_1 \cup A_2 \cup \cdots\cdots \cup A_k \quad , \quad n = \sum_{i=1}^{k} n_i \qquad (3\text{–}4)$$

where obviously $1 \leqq k \leqq n$.

" *A finite-dimensional vector space is decomposed to an arbitrary number of components, so far as the number remains within the dimention-number of the space. The sum of dimension-numbers of the components is equal to the dimension-number of the space.*"

When $\mathfrak{A}$ is decomposed according to formula (3–4), the relation

$$\alpha = \alpha_1 + \alpha_2 + \cdots\cdots + \alpha_k \quad \alpha \epsilon \mathfrak{A}, \quad \alpha_i \epsilon A_i \quad (i = 1, 2, \cdots\cdots, k) \tag{3–5}$$

holds uniquely for given α. If not so, $\alpha = \sum^{k} \alpha_i = \sum^{k} \alpha'_i \quad \therefore \quad \sum^{k} (\alpha_i - \alpha'_i) = 0$ Because $\alpha_i - \alpha'_i \epsilon A_i$ and because $\{A\}$ is independent, $\alpha_i - \alpha'_i = 0$. $\therefore \alpha_i = \alpha'_i$ from the above mentioned character 4). Hence, α_i corresponds uniquely to α given in $\mathfrak{A}$, according to formula (3–5). By making α correspond to α_i, a homomorphic mapping[1),3)] of $\mathfrak{A}$ to A_i is obtained. " *A_i is homomorphic to $\mathfrak{A}$.*" α_i is called as the " *component* " of α in direction to A_i or the " *projection* " of α in A_i.

These general characters of the vector space will be applied to the electric field $\bar{\mathfrak{P}}$.

The extension $\mathfrak{P}$ of $\bar{\mathfrak{P}}$ is a n-dimensional vector space, and is decomposed to k-components $(1 \leqq k \leqq n)$ as

$$\mathfrak{P} = \mathfrak{P}_1 \cup \mathfrak{P}_2 \cup \cdots\cdots \cup \mathfrak{P}_k \quad , \quad n = \sum_{i=1}^{k} d\mathfrak{P}_i \tag{3–6, 7}$$

The component p_i of $p \epsilon \bar{\mathfrak{P}} \subset \mathfrak{P}$ in direction to $\mathfrak{P}_i$ is determined uniquely and the formula

$$p = p_1 + p_2 + \cdots\cdots + p_k \tag{3–8}$$

holds. The set $\bar{\mathfrak{P}}_i$ consisting of p_i's corresponding to all p's in $\bar{\mathfrak{P}}$ is the " *component (field)* " of the field $\bar{\mathfrak{P}}$ in direction to $\mathfrak{P}_i$ or the " *projection* " of $\bar{\mathfrak{P}}$ in $\mathfrak{P}_i$. Then

$$\bar{\mathfrak{P}} = \bar{\mathfrak{P}}_1 + \bar{\mathfrak{P}}_2 + \cdots\cdots + \bar{\mathfrak{P}}_k \tag{3–9}$$

$$d\bar{\mathfrak{P}} = d\bar{\mathfrak{P}}_1 + d\bar{\mathfrak{P}}_2 + \cdots\cdots + d\bar{\mathfrak{P}}_k \tag{3–10}$$

hold, where the addition in formula (3–9) is defined as that between the elements of $\bar{\mathfrak{P}}_i$'s.

" *The electric field has its component in any given direction and of any lower dimension. It is reduced to the sum of its components.*"

As the special cases, the following two are the most important characters of the field.

1) The n-dimensional field is composed of n- one-dimensional fields.

2) The field is reduced to the sum of three-dimensional fields or to the sum of three-dimensional fields and a one- or two-dimensional one. The three-dimensional field is regarded as equivalent to that with a single electric dipole (Chapter 2), and the one- or two-dimensional field is considered to be a special field with a dipole. Hence, the electric field may be regarded as equivalent to that with electric dipoles.

In connection with the concept " *component of the field* ", the following results are interesting.

An electrocardiogram, a vector in the vector space (Chapter 2), has hitherto been named as a " *scalar electrocardiogram* " and regarded as a component or a projection of some vectorial quantity. In the author's opinion, too, an electro-

cardiogram p may agree with such view. To say in other words,

"*An electrocardiogram p represents a one-dimensional component field of the field* $\overline{\mathfrak{P}}$."
Or this is said in catchy expession that *ELECTROCRADIOGRAM IS SCALAR.*

This is the result corresponding to the conventional view "scalar electrocardiogram", and the meaning is as follows. An element p^* of the principal ideal $\mathfrak{P}^*$ generated by p ($\mathfrak{P}^*=[p]$) is expressed as ap ($a\epsilon F$). Then an element p_1 of the one-dimensional component field $\overline{\mathfrak{P}}_1$ of $\overline{\mathfrak{P}}$, in direction to $\mathfrak{P}^*$, is expressed as $a'p$ ($a'\epsilon F$). Or projection $\overline{\mathfrak{P}}_1$ of the field is composed of elements proportionate to p.

On the other hand, a scalar electrocardiogram is usually thought to be deduced from a "*vectorcardiogram*", provided that the electric field is generated by a single electric dipole,[15] because a vectorcardiogram is in reality synthesized from three independent scalar electrocardiograms p^1, p^2 and p^3 by certain method. Generally to say, the vectorcardiography is based on the view, the "*vectorial electro cardiography*" in our terminology, that the electric field is to be reconstructed by three scalar electrocardiograms. Vectorcardiogram is a sort of "*vectorial electrocardiogram*", the combination of three basic scalar electrocardiograms. This view is surely true, so far as the equivalency of electric field on the body surface to the single dipole field holds. But no one knows whether the equivalency does hold or not. Then, if not so, what represents or means this vectorial electrocardiogram? This question is generally a very complicated one, but under the condition that the electric field is linear (Chapter 2), the following may be allowed to say.

"*A vectorial electrocardiogram represents a three-dimensional component of the electric field*", corresponding to the former result that a scalar electrocardiogram represents a one-dimensional component of the field. Thus, "*A vectorcardiogram represents a three-dimensional component of the electric field.*" Because an element of the three-dimensional component $\overline{\mathfrak{P}}_3$ of $\overline{\mathfrak{P}}$, in direction to $\mathfrak{P}^*$, is expressed as $a_1p^1+a_2p^2+a_3p^3$ (a_1, a_2, a_3 ϵF) as well as an element of the ideal $\mathfrak{P}^*=[p^1, p^2, p^3]$ generated by three scalar electrocardiograms p^1, p^2 and p^3, a vectorcardiogram (a sort of vectorial electrocardiogram) represents a three-dimensional component $\overline{\mathfrak{P}}_3$ of the field, and does no more than this. This is the law which sets limits quantitatively to the vectorcardiography. Various methods of deriving the vectorcardiogram only determine the direction of component field which the vectorcardiogram represents.

As to the concept component or projection, more concrete explanation is demonstrated in the next chapter (Chapter 4).

Chapter 4.

Isomorphic Image of the Electric Field

This chapter was prepared in order to make intuitive understanding of the structure of the field possible.

As to $\overline{\mathfrak{S}}$ and mapping-f in formula (2–2),[19] the following postulations may empirically be accepted easily.

1) $\overline{\mathfrak{S}}$ is a convex closed surface and does not cross any straight line at more than two points.
2) Mapping-f is one-to-one and bicontinuous.[5] In other words, f is a topological mapping.[5]

As the extension $\mathfrak{P}$ of the field $\overline{\mathfrak{P}}$ is a n-dimensional vector space, an isomorphic

correspondence[1),3)] between $\bar{\mathfrak{P}}$ and V_n is obtained. And

$$V_n = g(\bar{\mathfrak{P}}) \tag{4–1}$$

shows this correspondence, an example of which is shown when in formula (2–13)'[19)] $A(a_1, a_2, \ldots\ldots, a_n)$ is made to correspond to p. Particularly, the most important isomorphic correspondence is that which makes p correspond to its field-position-vector $P(p_1, p_2, \ldots\ldots, p_n)$. Such an isomorphic correspondence is obviously possible, because formula (2–13)'' means an automorphism in V_n. This relation is specially expressed as

$$V_n = \pi(\bar{\mathfrak{P}}) \tag{4–2}$$

From formula (4–1),

$$\bar{V}_n = g(\bar{\mathfrak{P}}) \tag{4–3}$$

holds, where $\bar{V}_n$ is called as an "*isomorphic image or g-image*" of the electric field $\bar{\mathfrak{P}}$. And from formula (4–2),

$$V_n^* = \pi(\bar{\mathfrak{P}}) \tag{4–4}$$

holds, where V_n^* is called as the "*π-image*" of $\bar{\mathfrak{P}}$. The π-image is a sort of the isomorphic image.

From formulas (2–2) and (4–3),

$$\bar{V}_n = gf(\bar{\mathfrak{S}}) \tag{4–5}$$

where $\bar{V}_n$ is called as a "*gf-image*" of the body surface $\bar{\mathfrak{S}}$. The mapping-gf is also a topological mapping, because f is topological and g is isomorphic.

For the purpose of intuitive understanding, the vector space V_n is discussed as a geometric space, regarding an element of V_n as a geometric point. As, from 1), $\bar{\mathfrak{S}}$ is a two-dimensional cycle in the three-dimensional space (solid space), and as the dimension does not alter[5)] under the topological mapping-gf, the isomorphic image $\bar{V}_n$ must be also a two-dimensional cycle.

"*An isomorphic image of the electric field is a two-dimensional cycle.*"

As was seen in Chapter 3, the field $\bar{\mathfrak{P}}$ is decomposed to an arbitrary number of component fields, where formula (3–9) and (3–10) hold. The intuitive structure of these components will be discussed by means of their images. From formulas (3–9), (3–10) and (3–6, 7),

$$\bar{\mathfrak{P}} = \bar{\mathfrak{P}}_1 + \bar{\mathfrak{P}}_2 \tag{4–6}$$
$$d\bar{\mathfrak{P}} = d\bar{\mathfrak{P}}_1 + d\bar{\mathfrak{P}}_2 \tag{4–7}$$
$$\mathfrak{P} = \mathfrak{P}_1 \cup \mathfrak{P}_2 \quad , \quad \mathfrak{P}_1 \cap \mathfrak{P}_2 = 0 \tag{4–8}$$
$$d\mathfrak{P} = d\mathfrak{P}_1 + d\mathfrak{P}_2 \tag{4–9}$$

hold. And from formula (3–8),

$$p = p_1 + p_2 \qquad (p \in \mathfrak{P},\ p_1 \in \mathfrak{P}_1,\ p_2 \in \mathfrak{P}_2) \tag{4–10}$$

holds uniquely for given p. When these formulas are mapped by g into V_n,

$$V_n = V_{n_1} \cup V_{n_2} \quad , \quad V_{n_1} \cap V_{n_2} = 0 \tag{4–8}'$$
$$n = n_1 + n_2 \tag{4–9}'$$

hold from formulas (4–8) and (4–9). And from formula (4–10),

$$v=v_1+v_2 \quad (v\epsilon V_n, \quad v_1\epsilon V_{n_1} \ , \ v_2\epsilon V_{n_2}) \tag{4–10}'$$

holds uniquely for given v. V_{n_1} and V_{n_2}, n_1-and n_2-dimensional vector spaces respectively, will be called geometrically as "n_1- and n_2-dimensional planes", respectively (a plane in usual sense is here a two-dimensional plane and a straight line is a one-dimensional plane). They intersect themselves at only one point O (origin).

As the sets $\bar{V}_{n_1}$ and $\bar{V}_{n_2}$ consisting of v_1's and v_2's, respectively, corresponding to all v's in $\bar{V}_n$ are of course isomorphic images of two component fields of the electric field, the problem is then reduced to find a geometric method to determine v_1 and v_2 from v given. If v_1 is regarded as a variable in the relation derived from formula (4–10)'

$$v-v_1\epsilon V_{n_2} \tag{4–10}''$$

the intersection of the plane V_{n_1} with locus V_x of v_1 which satisfies this relation, is the point v_1. And V_x is a plane $V_{n_2}{}^*$ containing the point v and parallel to V_{n_2}. Hence, the point v_1 is determined as the intersection of $V_{n_2}{}^*$ with V_{n_1}.

Similarly, the point v_2 is determined as the intersection of plane V_{n_2} with plane $V_{n_1}{}^*$[Note] containing the point v and parallel to V_{n_1}.

When the field is decomposed to k-components, the method to determine their images is reduced, by the following manipulation, to the above-mentioned case where the components are only two. The formulas (3–9) and (3–6) are modified as $\bar{\mathfrak{P}}=\bar{\mathfrak{P}}_i+\bar{\mathfrak{P}}'_i \quad (\bar{\mathfrak{P}}'_i=\bar{\mathfrak{P}}_1+\bar{\mathfrak{P}}_2+\cdots\cdots+\bar{\mathfrak{P}}_{i-1}+\bar{\mathfrak{P}}_{i+1}+\cdots\cdots+\bar{\mathfrak{P}}_k), \quad \mathfrak{P}=\mathfrak{P}_i\cup\mathfrak{P}'_i$. Then we get the relation $v=v_i+v'_i$. Thus, v_i is the intersection of plane V_{ni} with $(n-n_i)$-dimensional plane $V'_{ni}{}^*$ containing the point v and parallel to V'_{ni} or to $V_1, V_2, \cdots\cdots, V_{n-1}, V_{n+1}, \cdots\cdots, V_n$.

By virtue of the isomorphic image, the meaning of the expression "*component*" or "*projection*" may have become more familiar. The image of component is a geometric projection of the image of the electric field. Later, these will be explained more concretely in case of $n=3$.

Next, the image of "*sub-field*" will be demonstrated. Locus $\bar{\mathfrak{S}}'$ of a point, on $\bar{\mathfrak{S}}$, of which field-position-coordinate A satisfies the equation

$$p_T=A\cdot\bar{P}_T=0 \tag{4–11}$$

for a given time-position T, is known empirically to exist and to be a closed curve on $\bar{\mathfrak{S}}$ (an one-dimensional cycle). It is the "*transitional pathway*" called by Grant, R. P.[13),14)] or the "*straight line*" in the previous report.[18)] Hence, in the following formulas due to formulas (2–2) and (4–5),

$$\bar{\mathfrak{P}}' = f(\bar{\mathfrak{S}}') \tag{4–12}$$
$$\bar{V}_n{}' = gf(\bar{\mathfrak{S}}') \tag{4–13}$$

$\bar{\mathfrak{P}}'$ and $\bar{V}_n{}'$ are not void. $\bar{\mathfrak{P}}'$ is named as a "*sub-field*" of $\bar{\mathfrak{P}}$, and $\bar{V}_n{}'$, an one-dimensional cycle, is an isomorphic image of the sub-field.

"*An isomorphic image of the sub-field is an one-dimensional cycle.*"

And the formula (4–11) determines a $(n-1)$-dimensional sub-space (or hyperplane)

Note: The plane in this chapter is the subspace itself and it passes through the origin. But $V_{n_1}{}^*$, $V_{n_2}{}^*$ and $V_{ni}{}^*$ do not so exceptionally.

V_{n-1} in V_n [Note]. Hence,

$$\bar{V}'_n = \bar{V}_n \cap V_{n-1} \tag{4-14}$$

"*An isomorphic image of the sub-field is intersection of the image of the electric field with hyperplane.*"

The reason why $\bar{\mathfrak{S}}'$ was named as straight line in the previous report[18] is due to the fact that it is an "one-dimensional" cycle and that it has the similar characters with straight line in primary geometry because its image lies on a hyperplane.

By applying the above-mentioned general arguments to the practically most important three-dimensional field, more concrete explanation will be demonstrated here.

As the image $\bar{V}_3$ of the three-dimensional field $\bar{\mathfrak{P}}$ is a two-dimensional cycle, it is a closed surface in the solid space V_3. Then, when the π-image is adopted as the isomorphic one, it can be drawn really. And according to the previous report, $L=(L')A$, where L is the lead vector of $p \in \bar{\mathfrak{P}}$. So an isomorphic mapping is obtained by making p correspond to L. Then, the image by such mapping is no other than the "*image surface*" called by Frank, E[16]. But it is almost impossible to be drawn in reality.

As to the components, there are only two ways to decompose the three-dimensional field.

$$\bar{\mathfrak{P}} = \bar{\mathfrak{P}}_1 + \bar{\mathfrak{P}}_2 \qquad d\bar{\mathfrak{P}}_1 = 1 \ , \ d\bar{\mathfrak{P}}_2 = 2$$

and

$$\bar{\mathfrak{P}} = \bar{\mathfrak{P}}_1 + \bar{\mathfrak{P}}_2 + \bar{\mathfrak{P}}_3 \qquad d\bar{\mathfrak{P}}_1 = d\bar{\mathfrak{P}}_2 = d\bar{\mathfrak{P}}_3 = 1$$

At first, the former case is explained. V_{31} and V_{32} are a straight line and a plane in the solid space V_3, which intersect with each other only at origin O as shown in Fig. 1. Plane V_{32} and straight line V_{31}*, which is parallel to V_{31} and contains

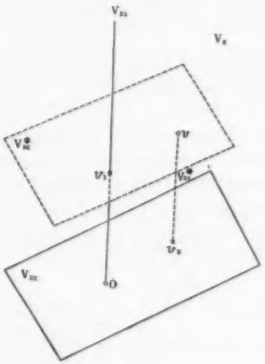


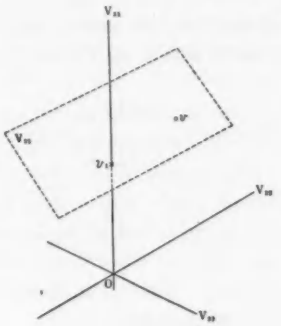
Fig. 1. Isomorphic images of component fields (Illustration-1).

a point v on the closed surface $\bar{V}_3$, determine the point v_2 as their intersection. Locus of the point v_2 when the point v moves on all over the surface $\bar{V}_3$, in other words, the projection of $\bar{V}_3$ on the plane V_{32}, is the image of the two-dimensional component

Note: Here, the correspondence of p to its field-position-coordinate A was used as g, but it is same the matter if another one was used.

field $\overline{\mathfrak{P}}_2$ of $\overline{\mathfrak{P}}$. It is a closed curve on the plane V_{32}. The intersection of straight line V_{31} with plane V_{32}*, which is parallel to plane V_{32} and contains the point v, is point v_1. Locus of v_1 or projection of $\bar{V}_3$ on the straight line V_{31}, is the image of the one-dimensional component field $\overline{\mathfrak{P}}_1$ of $\overline{\mathfrak{P}}$. $\bar{V}_3$ is the sum of $\bar{V}_{31}$ and $\bar{V}_{32}$.

In the latter case, in which the electric field is decomposed to three one-dimensional fields, the same is the matter (Fig. 2). Intersection of straight line V_{31} with plane V'_{31}*, which is parallel to straight lines V_{32} and V_{33} and contains v, is v_1. Points v_2 and v_3 are determined in the same way. Thus, $\bar{V}_3$ is decomposed to the images of three one-dimensional fields $\overline{\mathfrak{P}}_1$, $\overline{\mathfrak{P}}_2$ and $\overline{\mathfrak{P}}_3$ of the field $\overline{\mathfrak{P}}$.



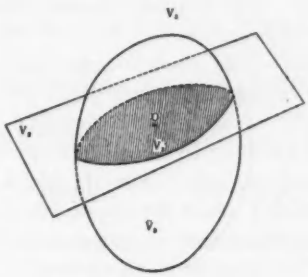


Fig. 2 (Left). Isomorphic images of component fields (Illutsration–2).
Fig. 3 (Right). Isomorphic image of sub-field.

The image of the sub-field is, of course, the intersection of closed surface V_3 with plane V_2 (Fig. 3). This is the image of the transitional pathway or of the straight line in the previous report.

Finally, some of the important characters of the mapping-π or the π-image will be demonstrated. This is a sort of isomorphic mapping and plays an important rôle in the present study because of the following characters. In general, π is used most commonly as an isomorphic mapping. Firstly, π makes potential p correspond to P (p_1, p_2, ..., p_n), an ordered set of potentials at n- basic time-positions,[18] which is possible and easy to be measured. So, π is the most practical among all isomorphic mappings. Secondly, P, image of p by π, may be regarded as an approximation of p. Being discrete values at n- basic time-positions of a continuous function p concerning variable time-position T, the components of p, p_1, p_2, ..., p_n, are able to represent approximately the function, if the basic time-positions are adequately selected. $P(p_1, p_2, ..., p_n)$ is called as the "*base of a potential p*" or as the "*base of an electrocardiogram p*".[Note] Then, the base P of an electrocardiogram p represents an approximation of p. In the previous reports,[17),18)] the ratio $p_1 : p_2 : ..... : p_n$ was called as the "*pattern of an electrocardiogram p*", and two electrocardiograms p and p' were "*similar*"[17),18)] if their patterns were equal ($p_1 : p_2 : ..... : p_n = p'_1 : p'_2 : ..... : p'_n$). This was due to the idea that the ratio approximately represented the configuration of electrocardiogram. In such mean-

Note: The "*base field matrix*" in the previous report[11)] is called also as the "*base of the electric field*" corresponding to the base of an electrocardiogram (see the next chapter).

ings, the mapping-π makes approximation of p. Thirdly, the image P plays an equivalent rôle to the lead vector (see the previous report).[18] In other words, P is an indicator of the site from which the electrocardiogram is recorded. So, P is named also as a "*field-position-vector*"[18] from this point of view. P is named as the "base of electrocardiogram" and as the "field-position-vector" according to its rôles.

Summary and Conclusion

(I) Decomposition of the Electric Field (Chapter 3)

(1) The concept "component (field) of the electric field" was introduced. The field has its own component in any direction and of any dimension.

(2) The electric field is decomposed to given-dimensional components, or it is reduced to the sum of the lower-dimensional (component) fields.

(3) From (2), the electric field is reduced to the sum of the three-dimensional fields or to the sum of the three-dimensional fields and a one- or two-dimensional one. The three-dimensional field is regarded as equivalent to that with a single electric dipole (Chapter 2), and the one- or two-dimensional field is considered to be a special field with a dipole. Thus, the electric field may be regarded as equivalent to that with electric dipoles.

(4) A scalar electrocardiogram represents a one-dimensional component (field) of the electric field. Or, in catchy expression, Electrocardiogram is Scalar.

(5) The scalar electrocardiogram has hitherto been thought, as literally shown, as a component or a projection of some vectorial quantity. The above (4) is the corresponding result to this conventional view. The result (4) is appeared to be inconsistent with the result in Part I that an electrocardiogram is a vector but this is not so.

(6) A vectorcardiogram represents a three-dimensional component (field) of the electric field, and does no more than this. This is the law which sets limits quantitatively to the vectorcardiography. Various methods of deriving vectorcardiogram can only determine the direction of the component field represented by the vectorcardiogram.

(II) Isomorphic Image of the Electric Field (Chapter 4)

(1) A geometric image of which structure is the same with that of the electric field, an "isomorphic image", is conceivable.

(2) An isomorphic image of the field is a two-dimensional cycle in the n-dimensional geometric space. The "image surface" called by Frank, E. is a sort of isomorphic image of the three-dimensional field.

(3) The isomorphic image of a component field is a geometric projection of the image of the electric field.

(4) The isomorphic image of so-called transitional pathway, a closed

curve on the body surface, is a one-dimensional cycle, and lies on a hyperplane. This determines the linear nature of the potentials on the pathway, and is the reason why the transitional pathway was named as straight line in the previous report.[18]

(The remaining part of this study will be reported in the succeeding issue.)

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Special Article

Lung Blood Volume in Acquired Valvular Diseases

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and Takuya SHIBA, M.D.

This report is concerned with the lung blood volume which should be divided into the true lung blood volume, the true left atrial blood volume and the left ventricular blood volume. Three blood volumes are estimated by following indicator dilution method; 1) dye (T_{1824}) is injected into the pulmonary artery by cardiac catheter and blood is sampled from the brachial artery, 2) injected into the left atrium by the puncture needle (percutaneous direct left atrial puncture) and sampled from the brachial artery, 3) injected into the pulmonary artery and sampled from the left atrium.

IN 1921, Stewart[1] injected saline solution intra-vascularly, and studied lung blood volume and cardiac output by measuring the circulation time. Later, Hamilton *et al.*[2)-4)] had applied dye injection method to the study of circulatory dynamics and thereafter this method has been used commonly.

In 1949, Ebert[5] and Boden *et al.*[6] inserted a catheter into the pulmonary artery and injected T_{1824} dye solution, and drew blood samples periodically from the femoral artery. Then, they plotted the values of dye concentration in blood to draw a curve and calculated mean circulation time. The blood volume from the pulmonary artery to the femoral artery was calculated by this mean circulation time and cardiac output was estimated by Fick's principle. They observed this value on normal individuals, patients with mitral stenosis and those with left ventricular failure and called it as "quantity of lung."

In 1952, Ball and his associates[7] calculated blood volume from cardiac output by Hamilton's injection method and considered it as the intrathoracic blood volume. They then applied this on the study of the patients with mitral stenosis.

Beside these, Doyle,[8] Chapman[9] and Hosono and others[10] also reported on the studies of so called lung blood volume measured by the dye injection method. However, in their experiments, the blood volume did not indicate the true lung blood volume. For example, the blood volume obtained by Ebert includes the blood volume in the left heart and aorta, and that by Ball

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includes the blood volume in the caval vein and right heart. Then Newman[11] established theoretical formula to calculate the lung blood volume provided that the intracardiac blood volume is small enough. However, even with this formula, it is impossible to calculate the true lung blood volume in cases with heart disease whose intracardiac blood volume is too large to be neglected.

The authors have studied on hemodynamics of acquired heart diseases by direct left heart puncture[12] and also revised the calculation of accurate lung blood volume. This article presents the method of measuring the mean circulation time from the pulmonary artery to the left atrium and from the left atrium to the brachial artery or to the femoral artery, together with our results of studies of true blood volume of the lungs and left heart.

Materials and Method

A total of 34 cases including 31 cases of mitral valve disease (MVD) and 3 cases of aortic valve disease (AVD), 2 cases of AVD complicated by mitral stenosis were studied (Table I). These types of valvular lesion were classified according to the results of hemodynamic analysis by direct puncture of left heart[13] and confirmed by operation.

Table I. Cases Examined by Dye-Dilution Method

1. Mitral valvular diseases	Case
Predominant stenosis group	
A type: Pure stenosis	13
B_I type: Stenosis predominant and insufficiency appreciable	6
B_{II} type: Insufficiency about as important as stenosis	1
Predominant regurgitation group	
B_{III} type: Insufficiency predominant with slight stenosis	3
C type: Pure insufficiency	8
2. Aortic valvular disease	
Aortic insufficiency	3
(Combined with mitral stenosis: 2)	
Total	34

Cardiac catheterization: Both right and left heart catheterization according to Cournand's method[14] and percutaneous direct left heart puncture by Bjoerk's method were used in all cases. In order to keep patient on supine position, we devised special bed with a hole through which the puncture needle could reach to the left atrium from the patient's back.

Dye injection method and blood sampling method: We applied 3-way to the manipulations of dye dilution method. 1) An injection of 3.5–4.0 ml. of 0.5% T_{1824} solution through F–8 catheter inserted into the stem of pulmonary artery and collection of blood samples from brachial artery at every 2 seconds, 2) An injection of 2.0–4.0 ml. of 0.8% T_{1824} solution through punctured needle into the left atrium and collection of blood samples from brachial artery at every 2 seconds, 3) An injection 2.5–4.0 ml. of 0.5% T_{1824} solution into pulmonary artery and collec-

tion of blood samples from left atrium at every 2 seconds. The interval between each trial of these 3 measurements was more than 10 minutes.

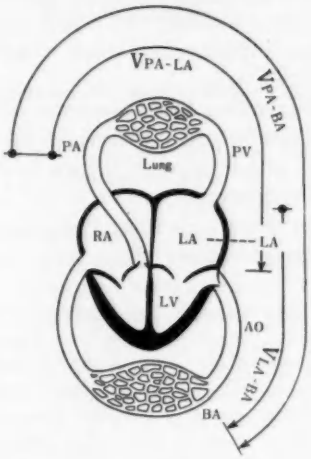

Fig. 1. Three manipulations of dye-dilution method.

Determination of the mean circulation time and calculation of the blood volume and cardiac output: After all blood samples were completely clotted, they were centrifuged and the serum was separated. Then this serum was diluted to 1/2–1/3 of the original concentration and its density was measured by the photometer. This density was plotted on semilogarithmic graph according to Hamilton's method and by connecting these points it was able to draw a dye dilution curve. Mean circulation time was obtained by the method dividing into 2 equal parts of dimensions. When the blood samples were drawn through a larger puncture needle than an ordinary indwelling needle, the value was corrected by following method.

corrected mean circulation time

= estimated mean circulation time − time through the puncture needle

time through the puncture needle (sec.)

$$= \frac{\text{volume of the puncture needle (ml.)} \times \text{sampling time (sec.)}}{\text{sampling blood volume (ml.)}}$$

volume of the puncture needle: 0.4 ml.

Blood volume from the site of injection to sampling position is calculated by the Stewart's formula and cardiac output by the Hamilton's formula. Each blood volume and cardiac output were expressed as individual body surface area.

Results

The blood volumes of each procedure are presented in Table II to IV.

Blood volume from the pulmonary artery to the brachial artery (V_{PA-BA}): Normal values obtained at our laboratory were 546–715 ml./M.^{2} averaging

666 ml./M.^{2} The value was 546–1,228 ml./M.^{2} in MVD, and 1,023–1,900 ml./M.^{2} in AVD. In MVD with predominant stenosis revealed 569–807 ml./M.^{2} (average 666 ml./M.^{2}) and insufficiency predominant group 702–1,228 ml./M.^{2} (average 964 ml./M.^{2}). These results were shown in Fig. 2, and can be rated in order of normal group—mitral stenosis—mitral insufficiency—aortic valvular disease.

Blood volume from the left atrium to the brachial artery (V_{LA-BA}): In MVD, the values were 241–420 ml./M.^{2} (average 305 ml./M.^{2}) in stenosis predomi-

Table II. Blood Volume, Mean Circulation Time and Cardiac Output Measured by Dye-Dilution Method in Cases of Predominant Mitral Stenosis

Case No.	Classification of valvular lesion	V_{PA-BA} ml./M.^{2}	V_{LA-BA} ml./M.^{2}	V_{PA-LA} ml./M^2.	MCT_1 sec.	MCT_2 sec.	MCT_3 sec.	CO_1 L./min.	CO_2 L./min.	CO_3 L./min.
127	A	615	—	481	13.9	—	10.9	3.3	—	3.3
134	A	569	—	280	12.7	—	7.9	3.5	—	2.8
135	A	784	—	562	12.4	—	8.5	5.4	—	5.6
145	A	687	—	494	12.7	—	9.5	4.9	—	4.9
148	B_I	807	420	514	17.1	7.8	9.5	4.2	4.9	4.9
158	B_{II}	642	282	—	22.6	10.4	—	3.0	2.8	—
54	B_I	682	269	507	11.9	6.6	10.3	5.5	4.9	4.9
160	A	706	339	412	21.4	12.0	14.6	3.0	2.6	2.6
162	B_I	715	352	—	28.8	12.1	—	2.0	2.3	—
172	A	623	303	441	12.5	6.1	8.2	3.8	3.8	3.8
175	A	664	245	467	7.9	3.7	5.1	7.9	6.3	8.6
178	A	642	311	487	10.5	5.1	8.0	4.9	4.9	4.9
181	B_I	652	259	496	15.1	6.0	11.5	3.6	3.6	3.6
188	B_I	614	241	—	12.8	5.0	—	3.6	3.6	—
189	A	651	317	467	8.2	4.4	6.5	6.2	5.6	5.6
192	A	642	261	482	9.7	4.0	7.3	3.0	3.0	3.0
194	A	683	304	503	11.4	5.2	8.5	5.4	5.3	5.3
196	B_I	668	369	472	21.6	8.5	10.8	2.9	4.1	4.1
197	A	619	290	—	11.4	5.3	—	4.6	4.6	—
199	A	665	320	454	16.2	6.4	8.5	3.1	3.7	4.0
Average		666	305	469*	18.5	6.7	9.1	4.2	4.1	4.4

Note:

V_{PA-BA}: caluculated blood volume from pulmonary artery to brachial artery by dye-dilution method, V_{LA-BA}: from left atrium to brachial artery, V_{PA-LA}: from pulmonary artery to left atrium.

MCT_1: mean circulation time from pulmonary artery to brachial artery measured by dye-dilution curve, MCT_2: from left atrium to brachial artery, MCT_3: from pulmonary artery to left atrium.

CO_1: cardiac output when measured MCT_1, CO_2: when measured MCT_2, CO_3: when measured MCT_3.

* 481 if No. 134 is omitted.

Table III. Blood Volume, Mean Circulation Time and Cardiac Output Measured by Dye-Dilution Method in Cases of Predominant Mitral Insufficiency

Case No.	Classification of valvular lesion	V_{PA-BA} ml./M.^{2}	V_{LA-BA} ml./M.^{2}	V_{PA-LA} ml./M.^{2}	MCT_1 sec.	MCT_2 sec.	MCT_3 sec.	CO_1 L./min.	CO_2 L./min.	CO_3 L./min.
124	B_{III}	830	—	549	21.4	—	15.8	3.0	—	2.7
126	C	1,055	—	566	35.4	—	24.2	2.3	—	1.8
128	B_{III}	1,012	—	543	22.2	—	16.8	3.9	—	2.8
138	C	892	—	512	10.7	—	5.2	6.7	—	7.9
151	C	1,228	820	—	24.3	15.7	—	4.5	4.6	—
154	C	1,080	593	661	30.1	13.5	15.0	3.0	3.6	3.6
157	C	702	381	475	12.3	6.7	8.3	5.3	5.3	5.3
166	C	923	594	527	18.3	10.4	9.4	4.7	4.7	4.7
171	C	958	552	551	15.2	8.0	9.8	6.1	6.6	5.4
173	C	1,019	533	582	12.5	6.2	7.4	7.1	7.6	7.0
174	B_{III}	905	640	521	29.2	23.2	8.9	2.7	2.4	2.4
Average		964	587	548	21.0	11.9	12.0	4.5	4.9	4.3

Note:

V_{PA-BA}: calculated blood volume from pulmonary artery to brachial artery, V_{LA-BA}: from left atrium to brachial artery, V_{PA-LA}: from pulmonary artery to left atrium.

MCT_1: mean circulation time from pulmonary artery to brachial artery, MCT_2: from left atrium to brachial artery, MCT_3: from pulmonary artery to left atrium.

CO_1: cardiac output when measured MCT_1, CO_2: when measured MCT_2, CO_3: when measured MCT_3.

Table IV. Blood Volume, Mean Circulation Time and Cardiac Output Measured by Dye-Dilution Method in Cases of Aortic Insufficiency Combined with Mitral Stenosis

Case No.	Classification of valvular lesion	V_{PA-BA} ml./M.^{2}	V_{LA-BA} ml./M.^{2}	V_{PA-LA} ml./M.^{2}	MCT_1 sec.	MCT_2 sec.	MCT_3 sec.	CO_1 L./min.	CO_2 L./min.	CO_3 L./min.
141	AI	1,900	—	655	21.2	—	5.5	9.4	—	10.5
161	AI+MS (A)	1,023	606	557	17.4	10.3	9.5	5.2	5.4	5.4
183	AI+MS (A)	1,276	825	685	19.3	12.0	10.0	5.9	6.1	6.1
Average		1,396	715	632	19.3	11.1	8.3	6.8	5.7	7.3

Note:

V_{PA-BA}: caluculated blood volume from pulmonary artery to brachial artery by dye-dilution method, V_{LA-BA}: from left atrium to brachial artery, V_{PA-LA}: from pulmonary artery to left atrium.

MCT_1: mean circulation time from pulmonary artery to brachial artery measured by dye-dilution curve, MCT_2: from left atrium to brachial artery, MCT_3: from pulmonary artery to left atrium.

CO_1: cardiac output determined by dye-dilution method when measured MCT_1, CO_2: when measured MCT_2, CO_3: when measured MCT_3.

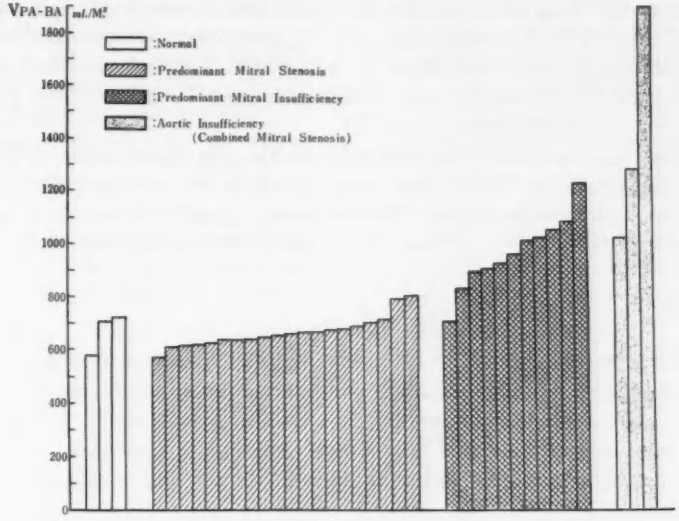

Fig. 2. Blood volume from pulmonary artery to brachial artery (V_{PA-BA}) in examined cases.

nant group. In insufficiency predominant group the values were 533–820 ml./M.² (average 587 ml./M.²). In AVD, values were 606–852 ml./M.² (average 715 ml./M.²).

Blood volume from the pulmonary artery to the left atrium (V_{PA-LA}); In MVD, values ranged from 412 to 661 ml./M.² with an expection of 280 ml./M.² Twenty cases of predominant mitral stenosis group revealed 412–562 ml./M.² (average 481 ml./M.²) with one exceptional case of 280 ml./M.² Predominant mitral insufficiency group ranged 475 to 661 ml./M.² (average 632 ml./M.²). In AVD, the values were 557–685 ml./M.² (average 632 ml./M.²). These values were quite similar to the previous results.

Discussion

The method of collecting samples through the needle in left atrium—

We aimed to discern whether V_{LA-BA} or V_{PA-LA} would include the left atrial blood volume or not, whether these calculated blood volumes would be influenced by the location of puncture needle in the left atrium.

In view of this, we attempted experimental studies on blood volume given by drawing blood through puncture needle in the left atrium. Under artificial respiration, thoracotomy was performed on adult dogs each weighing 7–10 Kg. and indwelling needles were inserted to the pulmonary artery (PA), pulmonary vein (PV), inflow portion of the left atrium (LA_i) and outflow portion of the left atrium (LA_o).

Then, (1) T_{1824} solution was injected into PA and blood samples were obtained from PV, LA_i, and LA_o, (2) T_{1824} solution was injected into LA_i and blood samples were obtained from PV, (3) T_{1824} solution was injected into LA_o and blood samples were obtained from PV and LA_i (Fig. 3). The results were shown in Table V to VII.

When T_{1824} solution was injected into PA, the blood samples from PV showed higher values before peak time at which dye concentration became maximum, but after peak time PV was lower, though LA_i and LA_o revealed equal values (Table V). When T_{1824} solution was injected into LA_i or

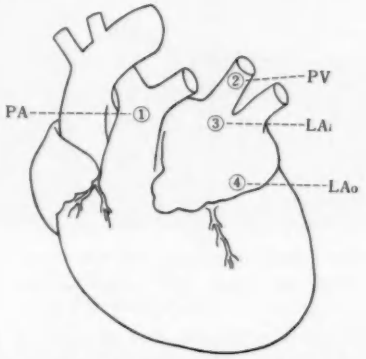

Fig. 3. Dye injection and/or blood sampling position by experimental studies.

Table V. Dye Concentration of the Blood Sampled Simultaneously from PV, LA_i and LA_o after Dye (0.5% T_{1824} Solution 1.0 ml.) Injection into Pulmonary Artery Trunk

A. Blood sampled before peak time

Dog No.	Peak time	Sampling time after dye injection	Blood sampling position		
			PV	LA_i	LA_o
1	2~4 sec.	2 sec.	6.0 mg./100 ml.	1.6 mg./100 ml.	1.6 mg./100 ml.
2	4~6 sec.	3 sec.	6.8 mg./100 ml.	4.8 mg./100 ml.	4.9 mg./100 ml.
3	4~6 sec.	3 sec.	7.7 mg./100 ml.	4.9 mg./100 ml.	4.7 mg./100 ml.
4	2~4 sec.	2 sec.	2.75 mg./100 ml.	2.05 mg./100 ml.	2.05 mg./100 ml.

B. Blood sampled after peak time

Dog No.	Peak time	Sampling time after dye injection	Blood sampling position		
			PV	LA_i	LA_o
5	2~4 sec.	5 sec.	0.8 mg./100 ml.	1.25 mg./100 ml.	1.25 mg./100 ml.
6	4~6 sec.	6 sec.	1.1 mg./100 ml.	2.85 mg./100 ml.	2.85 mg./100 ml.
7	4~6 sec.	7 sec.	0.7 mg./100 ml.	1.3 mg./100 ml.	1.4 mg./100 ml.
8	2~4 sec.	5 sec.	1.2 mg./100 ml.	2.6 mg./100 ml.	2.4 mg./100 ml.

Table VI. Dye Concentration of the Blood Sampled Simultaneously from LA_i and PV when Dye (0.005% T_{1824} Solution 0.2 ml.) Injected into LA_0

Dog No.	Blood sampling position	
	LA_i	PV
9	9.6 mg./100 ml.	0 mg./100 ml.
10	17.2 mg./100 ml.	0 mg./100 ml.
11	14.4 mg./100 ml.	0 mg./100 ml.

Table VII. Dye Concentration of the Blood Sampled Simultaneously from PV When Dye (0.005% T_{1824} Solution 0.2 ml.) Injected into LA_i

Dog No.	Blood sampling position
	PV
9	0 mg./100 ml.
10	0 mg./100 ml.
11	0 mg./100 ml.

La_0, dye was not found at PV (Table VI, VII). This fact indicates that when puncture needle is in the left atrium, the dye concentration in the left atrium will be given without being influenced by the position of the needle. Therefore, V_{LA-BA} and V_{PA-LA} measured by us can be considered to indicate the blood volume including the blood volume in the left atrium (Fig. 4).

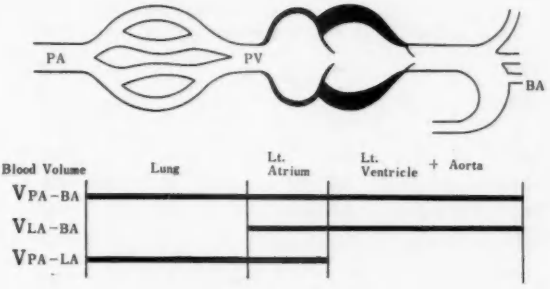

Fig. 4.

True lung blood volume—

V_{PA-LA} is a closer value to the real lung blood volume than V_{PA-BA} which has been used commonly. As we mentioned at the beginning of the discussion, it can be said that $V_{PA-BA}-V_{LA-BA}$ expresses the true lung blood volume because the blood volume from the left atrium to aorta is withdrawn. The result is shown in Table VIII. In MVD it ranged from 299 to 487 ml./M.^{2} (average 368 ml./M.^{2}), in predominant stenosis group from 299 to 419 ml./M.^{2} (average 361 ml./M.^{2}), in predominant insufficiency group from 265 to 487 ml./M.^{2} (average 385 ml./M.^{2}) and in AVD it was 417 and 451 ml./M.^{2} (average 434 ml./M.^{2}).

From these 3 values, we know that the lung blood volume has no great difference in each disease though it was little larger in AVD. When the relation of V_{PA-BA} and V_{LA-BA} was investigated, the results were as shown in

Table VIII. True Lung Blood Volume ($V_{PA-BA}-V_{LA-BA}$)

Case No.	Classification of valvular lesion	$V_{PA-BA}-V_{LA-BA}$ ml./m².
148	MS (B_I)	373
158	MS (B_{II})	360
54	MS (B_I)	413
160	MS (A)	367
162	MS (B_I)	366
172	MS (A)	320
175	MS (A)	419
178	MS (A)	331
181	MS (B_I)	393
188	MS (B_I)	373
189	MS (A)	334
192	MS (A)	381
194	MS (A)	379
196	MS (B_I)	299
197	MS (A)	309
199	MS (A)	345
	Average	360
151	MI (C)	408
154	MI (C)	487
157	MI (C)	311
166	MI (C)	329
171	MI (C)	406
173	MI (C)	486
174	MI (B_{III})	265
	Average	385
161	AI+MS (A)	417
183	AI+MS (A)	451
	Average	434

Fig. 5 and some correlation existed between these 2 volumes. The increased V_{PA-BA} was greatly influenced by increase in V_{LA-BA}.

Boden *et al.*[6] presumed that since so-called lung blood volume increased in mitral stenosis the pure lung blood volume was also supposed to be increased. Hosono[10] and Kattus *et al.*[15] also calculated the lung blood volume in acquired valvular diseases by Newman's formula and found no marked increase. However, their method is correct under the hypothesis that the ventricular blood volume is smaller enough than the lung blood volume. Therefore, their methods are not applicable in cases with valvular diseses.

In our series of measurements there were cases in which V_{LA-BA} was larger

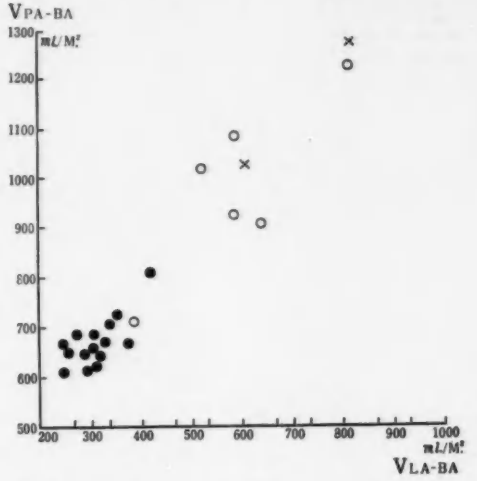

Fig. 5. Relationship between V_{PA-BA} and V_{LA-BA}.
●: Predominant mitral strenosis
○: Predominant mitral insufficiency
×: Aortic insufficiency with mitral stenosis

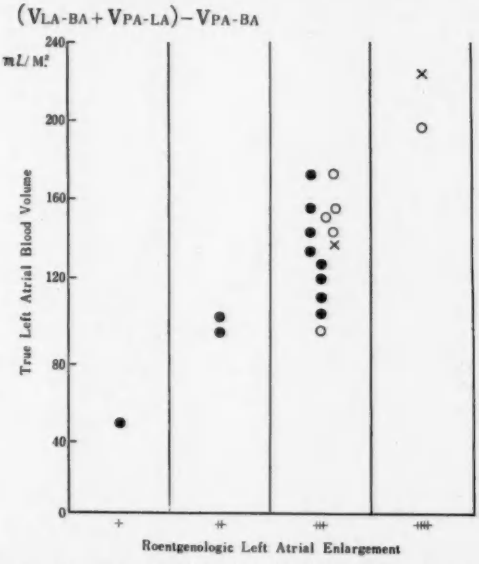

Fig. 6. Relation of true left atrial blood volume to roentgenologic left atrial enlargement.
●: Predominant mitral stenosis
○: Predominant mitral insufficiency
×: Aortic insufficiency with mitral stenosis

Table IX. True Left Atrial Blood Volume ($V_{LA-BA}+V_{PA-LA}-V_{PA-BA}$)

Case No.	Classification of valvular lesion	$V_{LA-BA}+V_{PA-LA}-V_{PA-BA}$ ml./M.^{2}
148	MS (B_I)	127
54	MS (B_I)	94
160	MS (A)	45
172	MS (A)	121
175	MS (A)	48
178	MS (A)	156
181	MS (B_I)	103
189	MS (A)	133
192	MS (A)	101
194	MS (A)	124
196	MA (B_I)	173
199	MS (B_I)	109
	Average	111
154	MI (C)	174
157	MI (C)	154
166	MI (C)	198
171	MI (C)	145
173	MI (C)	96
174	MI (B_{III})	256
	Average	171
161	AI+MS (A)	140
183	AI+MS (A)	234
	Average	187

than the calculated lung blood volume. Using direct method, our trials confirmed the fact which was presumed previously by these investigators.

True left atrial blood volume—

True left atrial blood volume can be calculated by subtraction of other items from assumption of each blood volume including left atrium. Namely, $(V_{PA-LA}+V_{LA-BA})-V_{PA-BA}$ equals the left atrial blood volume (Table IX).

When we examined carefully the degrees of dilution in the left atrium judged from X-ray findings,[16] there was a correlation between the amount of blood volume and the size of left atrium (Fig. 6).

Left ventricular blood volume—

It was impossible to calculate the true left ventricular blood volume by our method because the intra-aortic blood volume could not be excluded. This is due to the fact that $V_{PA-BA}-V_{PA-LA}$ reveals the blood volume in left ventricle

Table X. $V_{PA-BA}-V_{PA-LA}$ and ECG Findings in Cases of Mitral Valvular Disease

Case No.	Classification of mitral valvular lesion	$V_{PA-BA}-V_{PA-LA}$ ml./m².	ECG
127	A	134	RVH
178	A	155	RAD
181	B_I	156	RAD
192	A	160	RV-St
172	A	182	RVH
189	A	184	RAD
145	A	193	normal
196	B_I	196	RVH
175	A	203	normal
199	A	211	RVH
135	A	222	RVH
124	B_{III}	281	LV-St
134	A	289	RVH
148	B_I	293	LV-St
160	A	294	RVH
138	C	380	normal
174	B_{II}	384	LV-St
166	C	396	LV-St
171	C	397	LVH
154	C	419	LVH
128	B_{III}	469	LV-St
126	C	489	LV-St
173	C	537	LVH

RV-St: Right ventricular strain
RAD: Right axis deviation
RVH: Right ventricular hypertrophy
LV-St: Left ventricular strain
LVH: Left ventricular hypertrophy

and aorta. But we considered that what will express the blood volume instituted influence of the left ventricle. Now we compared these results with E.C.G. findings in order to investigate the states of the left ventricle. The results were shown in Table X. The tendency of increase in this value was noted in left ventricular strain and hypertrophy. Thereupon, in acquired valvular diseases, it could be possible to say that the cases with increased left ventricular load are also accompanied by increased values of these blood volumes.

Cardiac output during the studies—

During the manipulations, the patient was rested at supine position on comfortable bed, and cardiac output during the manipulations was calculated by dilution method and circulatory hemodynamic status was studied.

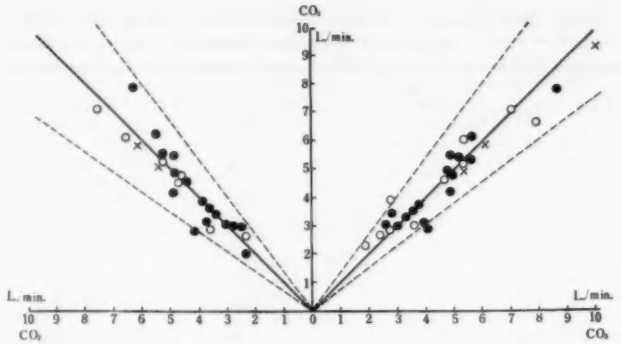

Fig. 7. Cardiac output during three manipulations of dye-dilution method.
●: Predominant mitral stenosis
○: Predominant mitral insufficiency
×: Aortic insufficiency combined with mitral stenosis

The results were as shown in right column of Table II to IV and the values measured at each stadium are in Fig. 7. There was no fluctuation exceeding 25%. According to Hamilton *et al.*, the fact that the cardiac output fluctuates within the range of 25% has been noticed already, and even though our studies were performed at rest and steady state, we will not hesitate to conclude that arithmetical calculation is possible from each measured value.

Summary

(1) We performed right heart catheterization and direct left atrial puncture. The calculated blood volume by dye dilution method was divided into 3 parts; i.e. the blood volume from the pulmonary artery to the brachial artery, from the left atrium to the brachial artery and from the pulmonary artery to the left atrium.

(2) The true lung blood volume, true left atrial blood volume and left ventricular-aortic blood volume were calculated by using above mentioned method of measurement. By this method, direct determination of the blood volume in the lung and left atrium became possible.

(3) The true lung blood volume does not reveal marked increase in acquired valvular diseases, and no marked difference in it was noticed among each type of valvular lesions.

(4) There was a relationship between the left atrial blood volume and the degree of dilatation of the left atrium determined by the X-ray findings.

(5) The comparison of the left ventricular-aortic blood volume and electro-cardiographic findings confirmed the fact that an increased load of left ventricle results in a increased blood volume.

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Case Reports

Hemoglobin M Disease

A Case Report

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Fuminobu MORI, M.D., Shunichi KODAMA, M.D.,
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CONGENITAL and chronic cyanotic diseases which has been regarded as morbus caeruleus in the past became enlightened in recent years from the pathoanatomical and hematological points of view.

In 1884, methemoglobinemia was distinguished from cyanotic congenital heart diseases by Francois. Since that time, more than 100 cases have been reported by many authors.[1] What had been reported as "chronische familiäre Methämoglobinämie" by Hörlein and Weber in 1948[2] was ascertained to be hemoglobin M disease due to abnormal hemoglobin.

In this paper a case with congenital cyanosis is described, which is considered, after an extensive examination, to be a hemoglobin M disease, the report of which is very rarely found in the literature up to this time.

Case Report

M. S., 6-year-old boy, was admitted to the Kurume University Hospital on May 30, 1959, with a chief complaint of cyanosis.

Birth was normal at full term. He has been found to be pale or cyanotic since his birth.

At the age of 3, he was diagnosed as having no cardiovascular abnormality. During his infancy, he has never had dyspnea, palpitation nor increasing of the grade of cyanosis on exercise.

He has no siblings. Father is 35-year-old bamboo worker and well. Mother, 31-year-old, has been pulmonary tuberculosis, having a partial lobectomy in 1958. Both parents have no cyanosis or cardiovascular diseases. All relatives were observed with on cyanosis (Fig. 1). He has had a measles at the age of 4. He has never experienced gastrointestinal disorders and there was no history of exposure to toxic agents.

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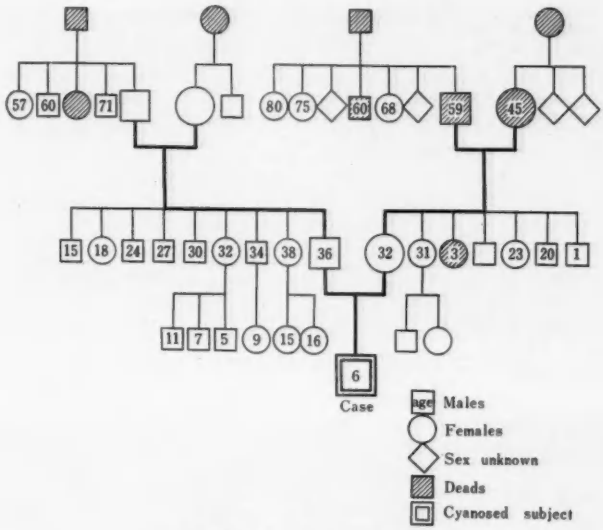


Fig. 1. Family tree of M.S.

Clinical Pictures:

Height 105.1 cm., weight 16.6 kg. He is well developed and no mental disturbance was found. Colour of the skin was bluish. Moderate cyanosis on the nailbeds and mucous membranes was present. No clubbing of the fingers was present. Purpura and exanthema were absent. Axillary temperature was 36.8°C.

Pulse was regular and the rate was about 90 per minute, with a moderate tension. Blood pressure was 100/60 mm.Hg, without significant difference between the right and left arm. Pupills was round and regular. Light reflex was normal. Movement of the eyeball was normal. Palpebral conjunctiva and mucous of mouth was slightly anemic in colour, but there was no hemorrhage. Tonsills were slightly hypertrophied. Chest was not remarkable. The percussion over the lung fields revealed no abnormality and the breath sound was normal. Right lower border of the lung resonance was on the sixth rib and its respiratory movement was normal. Cardiac dullness extended slightly to the right from the sternum. Upper dullness was at the level of the third rib. Left border extended slightly to the left midclavicular line. Heart sound at the apex was clear. Soft systolic murmur was present over the pulmonic area. Pulmonic second sound was accentuated. Abdomen was flat and soft. No organs, masses or rigidity were palpable. Patellar tendon reflex was intact and no pathological reflexes were noted. There was no edema of the lower extremities.

Clinical Findings and Diagnosis:

As indicated in Table I, there was no polycythemia but slight anemia in hematological study. Examinations of urine and feces were normal. Liver function,

Table I. Laboratory Findings

Urinalysis			
Reaction	acid	Sugar	(−)
Colour	normal	Bilirubin	(−)
Albumin	(−)	Porphylline	(−)
Urobilinogen	normal		
Feces			
Occult blood	(−)		
Parasite ova	(−)		
Liver function			
Kunkel		2.2 u.	
Thymol turbidity test		2.3 u.	
Takata reaction		(−)	
Icteric index		6.0	
Non protein nitrogen		39 mg./100 ml.	
Serum Wassermann reaction		negative	
Hematology			
R.B.C.		405×10^4	
Hemoglobin		75% Sahli	
		12.2 Gm./100 ml.	
Hematocrit		31%	
Reticulocytes		0.46%	
Platelets		186,300/mm.^{3}	
Bleeding time		1'30''	
Coagulation time		2'30''	
		9'30''	
W.B.C.		6,400	
Differential count			
Neutrophils		26%	
Eosinophils		3%	
Basophils		0%	
Lymphocytes		65%	
Monocytes		6%	
Plasma cells		0%	
Peroxydase reaction		normal	
Blood Chemistry			
Total protein	7.0 Gm./100 ml.	Total lipids	468 mg./100 ml.
Fraction		Total cholesterol	193 mg./100 ml. (Kieth)
Albumin	50.5%		
α_1-Globulin	5.7%	Lipoprotein β/α	1.79
α_2-Globulin	12.4%	Lipids in lipoprotein	169 mg./100 ml.
β-Globulin	12.4%	Na	140.0 mEq./L.
γ-Globulin	19.0%	K	6.4 mEq./L.
A/G ratio	1.02%		

total protein, protein fraction, albumin-globulin ratio, total lipids and total cholesterol were all within normal limits. Electrocardiogram (Fig. 2) was normal.

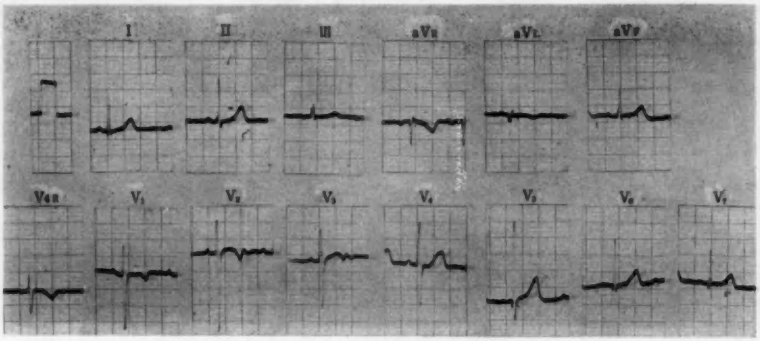


Fig. 2. Electrocardiogram of M.S. (June 11, 1959)

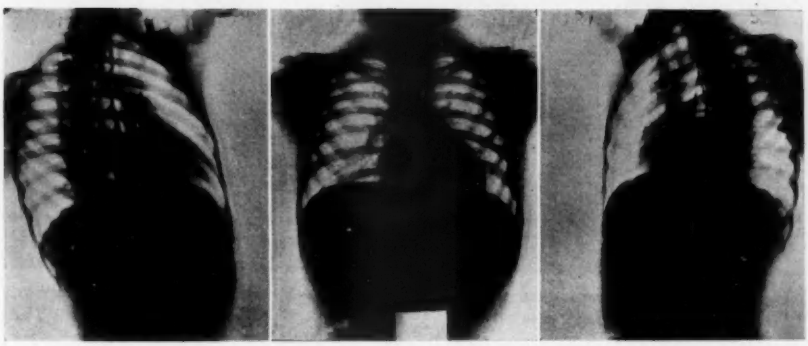
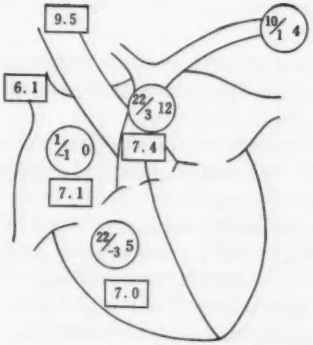


Fig. 3. Right anterior oblique, posteroanterior and left anterior oblique chest films of patient M.S.



Arterial blood O_2 capacity 12.3 Vol.%
Arterial blood O_2 saturation 77.2%

Fig. 4. Circulatory dynamics.

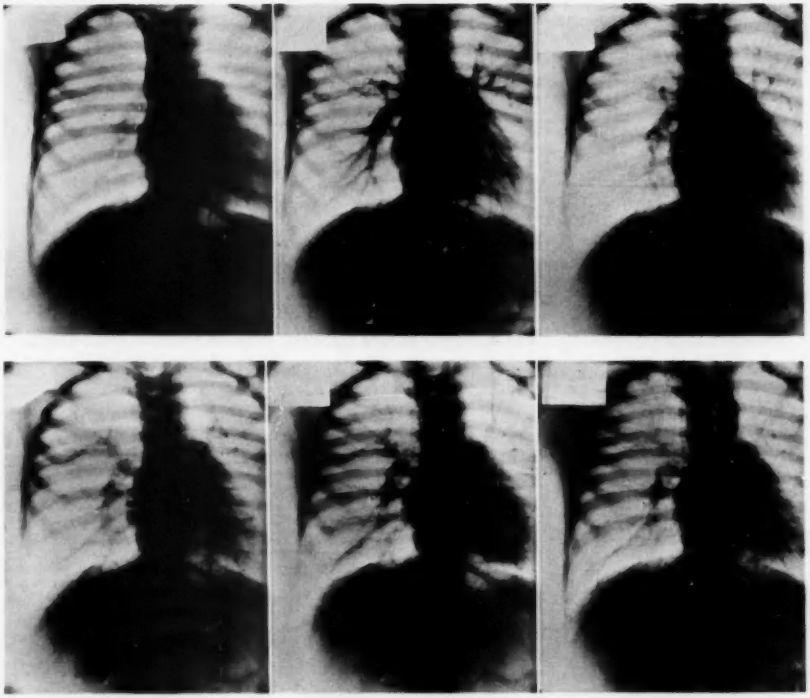


Fig. 5. Angiocardiogram taken one film per second using 20 ml. of 76 per cent Urographin,

Chest X-ray films (Fig. 3) showed no pathological findings. Intracardiac catheterization was performed under suspision of congenital heart disease because of existing cyanosis (Fig. 4). As indicated in Fig. 4, oxygen capacity was 12.3 Vol. per cent and oxygen saturation was 77.2 per cent. No abnormality was present in angiocardiogram (Fig. 5).

The venous blood was chocolate brown in colour, and the unusual colour was not altered by shaking it in the presence of air. Serum was clear and icteric index was 6.0.

Methemoglobinemia was suspected from the results of spectrophotometric and chemical studeis by the methode of Evelyn and Malloy,[3] but no increased methemoglobin or sulfhemoglobin was found in the blood. Two mg. of methylene blue (1 per cent solution) per kilogram of body weight given intravenously at slow rate over a period of 5 minutes[4],[5] and ascorbic acid given orally from 200 to 300 mg. a day during about one month were ineffective in decreasing the cyanosis.

" Abnorme Methämoglobinämie " reported by Hörlein and Weber in 1948[2],[6] having been suspected, spectrophotometrical examination of hemoglobin M was made in accordance with the method of P. Gerald.[7]

Heparinized blood obtained by venipuncture was centrifuged. After washing several times with physiological saline solution, red cell was hemolyzed with ad-

dition of distilled water and toluen, and the stroma was removed by high speed centrifugation. Thus, about 10 per cent hemoglobin solution (untreated hemolysate) was made.

Spectrophotometric studies were performed of this solution after treating by following methods with EPS-2 type Hitachi Recording Spectrophotometre.

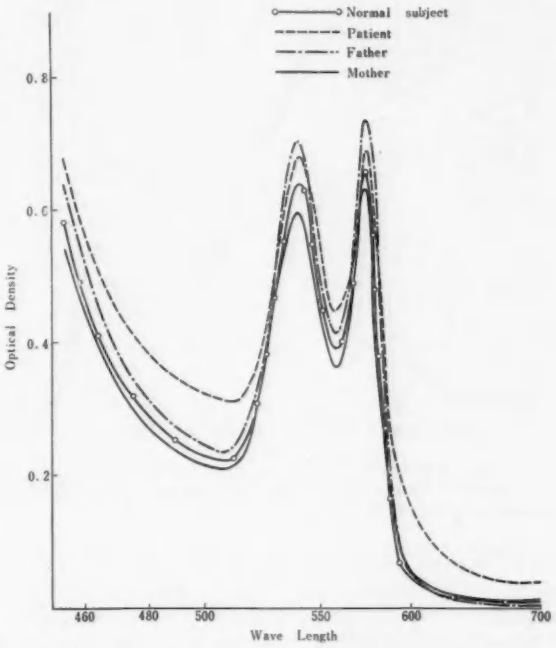


Fig. 6. Spectral curves of untreated hemolysates in M/15, Ph 6.5 sodium phosphate buffer.

Spectroscopy of the untreated hemolysate is shown in Fig. 6. Immediately after clarification by high speed centrifugation, the spectral absorbtion cuve of the hemolysate in M/15 phosphate buffer (pH 6.5) was obtained. Only the normal maxima for oxyhemoglobin (at 542 and 577 mμ) were present in the visible portion of the spectrum, these maxima were indistinguishable in their location from those of normal oxyhemoglobin. There was no peak at 630 mμ. But in the hemolysate of the patient there were 2 slight inflictions at about 500 and 600 mμ, and these spectral characteristics suggested the presence of abnormal pigment and were in agreement with the visual impression of the blood.[8]

Spectral curves of acid methemoglobin form is shown in Fig. 7. This form was prepared by oxidation of untreated hemolysate with potassium ferricyanide. These spectral curves showed a remarkable difference from that of the patient and of normal individual. In the hemolysates of normal subject and both parents of the patient, oxyhemoglobin peaks at 542 and 577 mμ were absent and the peaks due

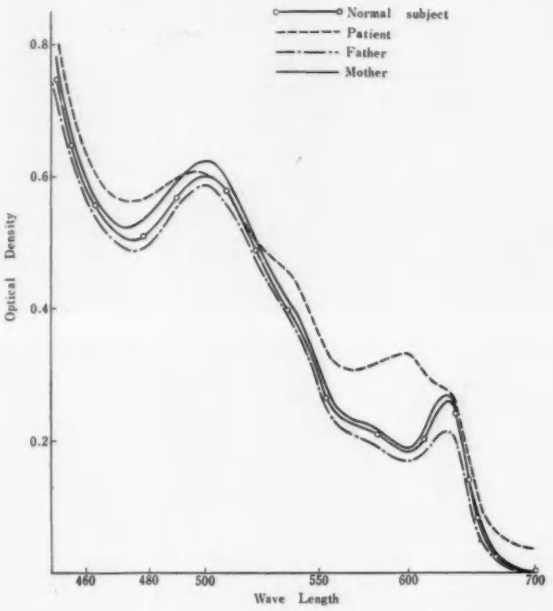


Fig. 7. Spectral curves of methemoglobin prepated by oxidation with potassium ferricyanide in M/15, Ph 6.5 sodium phosphate buffer.

to the presence of normal methemoglobin at 500 and 630 mμ became apparent after the treatment. The failure of the peak to appear at 630 mμ after oxidation of the oxyhemoglobin of the patient indicated that his methemoglobin differed from this derivative of normal hemoglobin in its spectral characteristics. This spectral curve closely resembles the curve reported by Hörlein and Weber[2),6)] or Kiese *et al.*[9)] Hemoglobin M content was determined by the method of P. Gerald[7)] as 77 per cent.

The spectral curves produced by the addition of neutralized sodium cyanide to the solution of Fig. 7 are shown in Fig. 8. There was no significant difference between the patient and the normal subjucts.

The alkali-resistant fraction was determined by the technic of Singer *et al.*[10)] and its values were within normal limits.

Comment

" Hemoglobin M disease " is a syndrome characterized by hereditarily transmitted cyanosis in absence of increased amounts of reduced hemoglobin of " normal " methemoglobin.[7)] Usually, cyanosis is attributed to the increase in the reduced hemoglobin produced from cardiac or pulmonary diseases. The colour of cyanosis is dependent upon the absolute amount of reduced hemoglobin and not upon the relative amounts of oxyhemoglobin

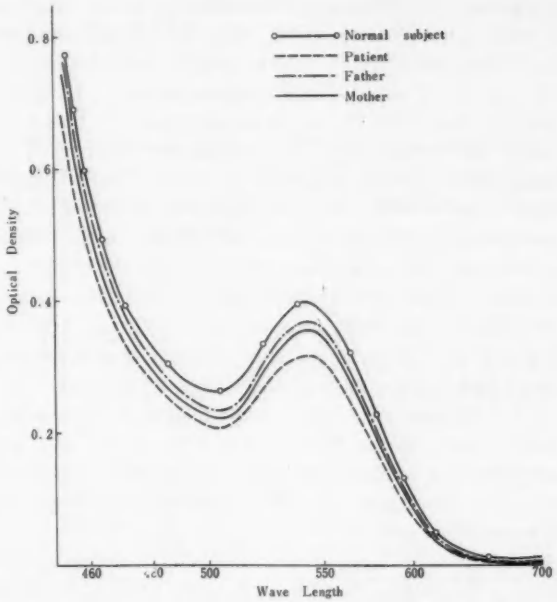


Fig. 8. Spectral curves of cyanmethemoglobin prepared by addition of neutralized sodium cyanide in M/15, Ph 6.5 sodium phosphate buffer.

and reduced hemoglobin.[11] About 5 Gm. of reduced hemoglobin per 100 ml. of blood is required to produce recognizable cyanosis.[12]

In our case, the only positive finding was the decrease in arterial blood oxygen capacity and oxygen saturation. There was no other finding in physical examination, ECG, fluoroscopic studies and intracardiac catheterization. So there was no evidence of any organic disorders.

In cyanosis due to abnormal pigments within the red cell, 1.5 Gm. of methemoglobin per 100 ml. of blood,[4] 15 per cent of total pigment of methemoglobin,[5] or 0.5 Gm. of sulfhemoglobin per 100 ml. of blood cause cyanotic hue.[4] A considerable amount of research has been reported on the methemoglobinemia—idopathic and secondary[4),5),13)-17)]—and about 100 cases have been observed in Europe and America.[1]

In this report of ours, as the plasma was clear and its protein fraction was normal, hemolysis and abnormal serum pigments were excluded as causes of the cyanosis. The whole blood was grossly chocholate brown and when shaken in air for 15 minutes, it remained dark. Spectrophotometric studies about this blood were made by the method of Evelyn and Malloy[3] under suspicion of methemoglobinemia, but neither methemoglobin nor sulfhemoglobin were present. Methylene blue injected intravenously and ascorbic acid given orally[2),4),5),18)] did not result in a dicrease of the cyanosis. These findings

excluded a possibility of methemoglobinemia.

It was Hörlein and Weber (1948) who first found methemoglobin with unusual spectral characteristics[2),6)] in a German family exhibiting a dominant transmission of a cyanotic condition for 4 generations. In their investigation they emphasized the facts that "neue Methämoglobin" had a new maximum of optical density at 600 mμ of wave length and that they had failed to detect methemoglobin by the method of Evelyn and Malloy which was dependent on the disapperance of a maximum at 630 mμ after chemical treatment. By interchanging the heme and the globin with the corresponding components of normal methemoglobin, they found the abnormality exist in the globin fraction. This hemoglobin was designated as hemoglobin M by Karl Singer in 1955.[19)] In 1956, another case of this hemoglobinopathy was reported by Kiese *et al.* It was observed that oxygen saturation of the hemoglobin was normal and the speed of reduction of hemiglobin was same as that of normal hemiglobin, but the oxygenation of hemoglobin by oxygen was 2 times faster than normal.[9)]

In our case it was a matter of much interest that in spite of the absence of cardio-respiratory disorders, oxygen capacity and oxygen saturation of arterial blood were decreased.

In 1957 Gerald *et al.*[8)] discovered a family of German extraction in New England presenting a cyanotic condition in at least 4 generations, and separated the hemoglobin of patient to hemoglobin A and hemoglobin M by starch electrophoretic technic of Kunkel.[20)] Piscotta *et al.* in the same year found a Swiss family with hemoglobin M defect.[21)] A 33-year-old woman of the family with cyanosis since birth had splenomegaly and mild hemolytic anemia. Paper electrophoresis of the hemoglobin showed 2 clear cut components—fast and slow electrophoretic migrations. He stated also that the properties of hemoglobin M included slow electrophoretic migration and inability to transport oxygen.

About the foregoing case Gerald gave additional reports of investigation in 1958.[7)] He reported that relative concentration of hemoglobin M was 30 per cent of the total hemoglobin. He classified hemoglobin M according to difference of reaction of hemoglobin M on cyanide.

The alkali-resistant fraction was found within the normal limits by the technique of Singer *et al.*[10)] in our case, but Piscotta *et al.* found a hemoglobin F content of 11 per cent of total hemoglobin in his case,[21)] and Gelard found a hemoglobin F content of 1.4 per cent in his case.[7)]

Hemoglobin M disease is a kind of molecular disease,[19),22),23)] since spectroscopically and electrophoretically anomalous behaviour is attributable to an abnormality of globin. So a hereditary observation is necessary with a person about the study. Hörlein and Weber, Piscotta *et al.*, Gerald *et al.* found clear dominant hereditary pattern in each case, but such could not be found in our case. Further studies in this point are necessary.

In Japan "Nigramia hereditaria" first discribed by Tamura and Taka-

hashi[24),25)] has been given attention in relationship of hemoglobin M diseses recentry.

Summary

We examined a cyanotic patient considered as congenital heart disease and found that it was due to hemoglobin M disease spectrophotometrically. Hemoglobin M was 77 per cent of the total hemoglobin. We could not find the hereditary pattern in our case.

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Annular Constrictive Pericarditis
A Case with Functional Pulmonary and Mitral Stenosis

Tsuguya SAKAMOTO, M.D., Nobuyoshi KAWAI, M.D.,*
Jugoro TAKEUCHI, M.D.,** *and* Hideo UEDA, M.D.***

IN general, constrictive pericarditis is anatomically characterized by the pericardial adhesions and constricting scar or calcification on the surface of the free wall of the ventricles, although it may be denser in some areas than the other. This results in the impediment to the diastolic filling of the ventricle and is responsible for the various clinical signs of this entity such as the proto-diastolic extra sound.[1)-3)] However, the pericardial calcification may be very pronounced exclusively in the atrioventricular groove and may produce the unique clinical manifestations.

This report illustrates a case of chronic constrictive pericarditis which has an annular pericardial calcification constricting the atrio-ventricular groove and producing the murmurs of pulmonary and mitral stenosis.

Case Report

S. N., a 15-year-old boy, was admitted to Tokyo University Hospital on February 19, 1960, because of edema, ascites, tachycardia, tachypnea and dyspnea. There was no definite past or family history of tuberculous disease. The onset of these symptoms was obscure, but at the age of 4, high fever, edema and dyspnea developed after the fracture of the pelvic bone. He was treated for about 7 months as post-traumatic pleurisy, with improvement. At the age 10, he suffered from osteomyelitis of the left upper arm, treated for one month and recovered. Since then edema re-appeared on the legs, and thereafter ascites appeared and waned or waxed repeatedly. About 3 years ago, he had no cardiac murmurs but the triple rhythm characteristic to constrictive pericarditis was noted by a phonocardiologist**** and more extensive examinations were recommended. Since January 1960, tachypnea and dyspnea gradually appeared and the above-mentioned symptoms progressively became severe.

The physical examination on admission revealed generalized edema and pronounced ascites. Respiratory rate was 22 and appeared markedly dyspneic. The neck vein was distended even in a sitting position. The pulse was regular with

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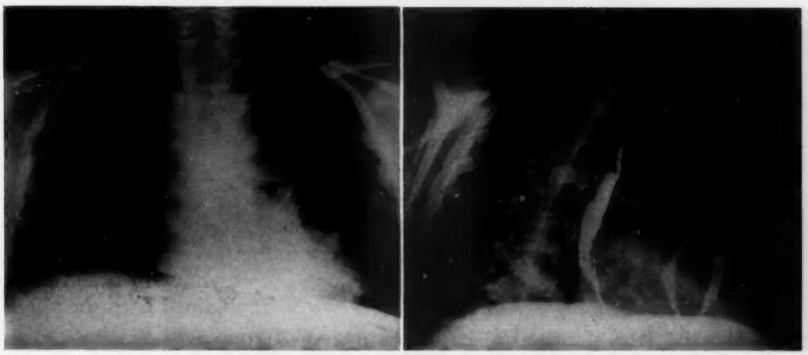
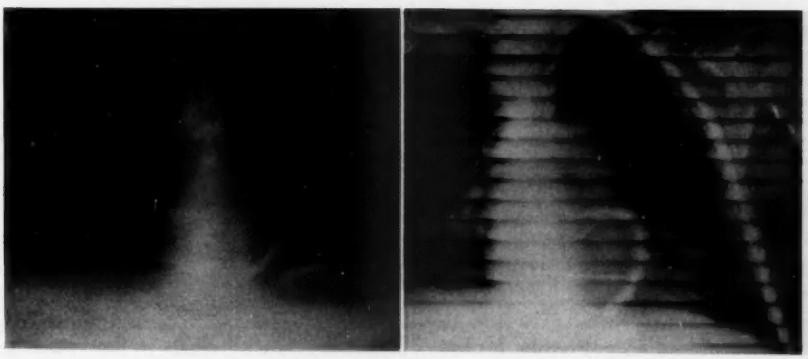
the rate of 120. The blood pressure was 104/74 mm. Hg. The cardiac dullness was moderately enlarged to the left side. On auscultation, there were loud (grade IV) systolic murmur at the pulmonic area and a faint and short apical rumbling murmur with a definite extra sound. Moreover, on the lateral to the apex, a musical systolic murmur (grade II) was heard, which completely disappeared later. Abdomen was swollen markedly and distended due to the pronounced ascites. Striae cutis were seen on the lower abdomen. The liver and the spleen were not palpable. The venous pressure was 230 mm. in water.

X-ray film of the chest revealed the enlargement of the heart and an annular calcification (Fig. 1 a, b). The annular ring was better recognized by high tension X-ray film (Fig. 2 a). Slight pulmonary congestion was noted. Roentgenkyomogram revealed no significant limitation of the movement in the left ventricular border. The annular ring and the right ventricular border were moderately limited



a. b.

Fig. 1. Roentgenogram of the chest. **a**: Posteroanterior, **b**: Right anterior oblique position. Details in text.



a. b.

Fig. 2. **a**: High tension X-ray film of the chest. **b**: Roentogenkyomogram. Details in text.

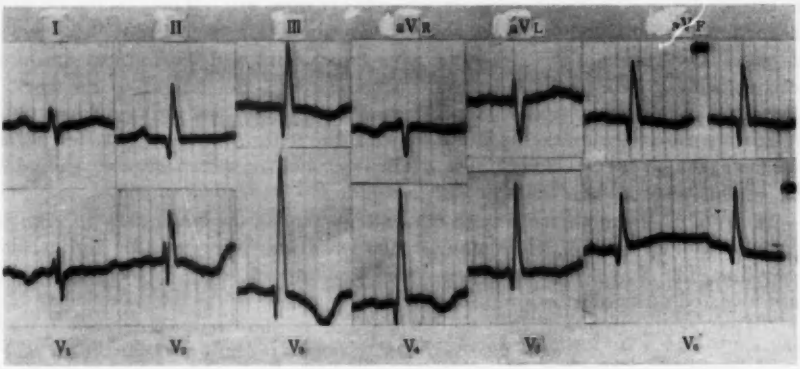


Fig. 3. Electrocardiogram taken on the time of admission. Inversion of T-wave in leads II, III, aVF, and V_1–V_5. Notching of P-waves. Relatively left axis deviation of the P-wave compared with the axis of ventricular complex. Negative P-wave in lead V_1. The Q-wave in leads II, III, aVF and V_4–V_6 accompanying the T-wave change. Bizarre QRS complex in leads V_1 and V_2.

in their movements (Fig. 2 b). Electrocardiogram showed the sinus tachycardia with the flattened or inverted T-waves in all leads (Fig. 3). The phonocardiogram (Fig. 4) revealed the above-mentioned auscultatory findings, but it was not clear whether the diastolic extra sound was protodiastolic or presystolic in time because of the severe tachycardia (the rate of 146). The results obtained from the phonocardiogram will be discussed later.

Main laboratory findings were as follows: a) marked hypoproteinemia with the total serum protein level of 3.8 Gm./100 ml. (albumin=45.5%; globulin: α_1=7.7, α_2=15.7, β=18.7, γ=11.5%, and A/G-ratio=0.82). b) Blood cell counts; Hb.=84%, RBC=420×10^4, and WBC=9,000. c) Serum Na=141 mEq./L., K=4.0 mEq./L., and Cl=108 mEq./L. d) Liver function tests revealed slight disturbances.

Hospital course: After his admission, he was given diuretic with marked improvement. The fever retired by a daily dose of 1 Gm. of tetracycline. Hypoproteinemia was treated with the infusion of plasma and amino-acid preparation. In the beginning of April, total serum protein was increased up to 5.0 Gm./100 ml. However, diuretics soon became ineffective and the total protein level returned to the initial value of 3.7 Gm./100 ml. on April 21. The ascites re-increased, and the venous pressure gradually elevated and reached up to the value of 280 mm. in water. The murmur with the musical quality at the 5th intercostal space on the left mid-axillary line disappeared as already mentioned when the fever retired. The mid-diastolic rumbling murmur was clearly seen in phonocardiogram throughout the course whenever relatively slow heart rate was present. It starts immediately after the diminished protodiastolic extra sound and once increases its intensity and then decreases before the 1st heart sound. The pulmonic ejection-type murmur remains in its intensity.

On April 27, he was transfered to Surgical Department of Prof. Kimoto for an

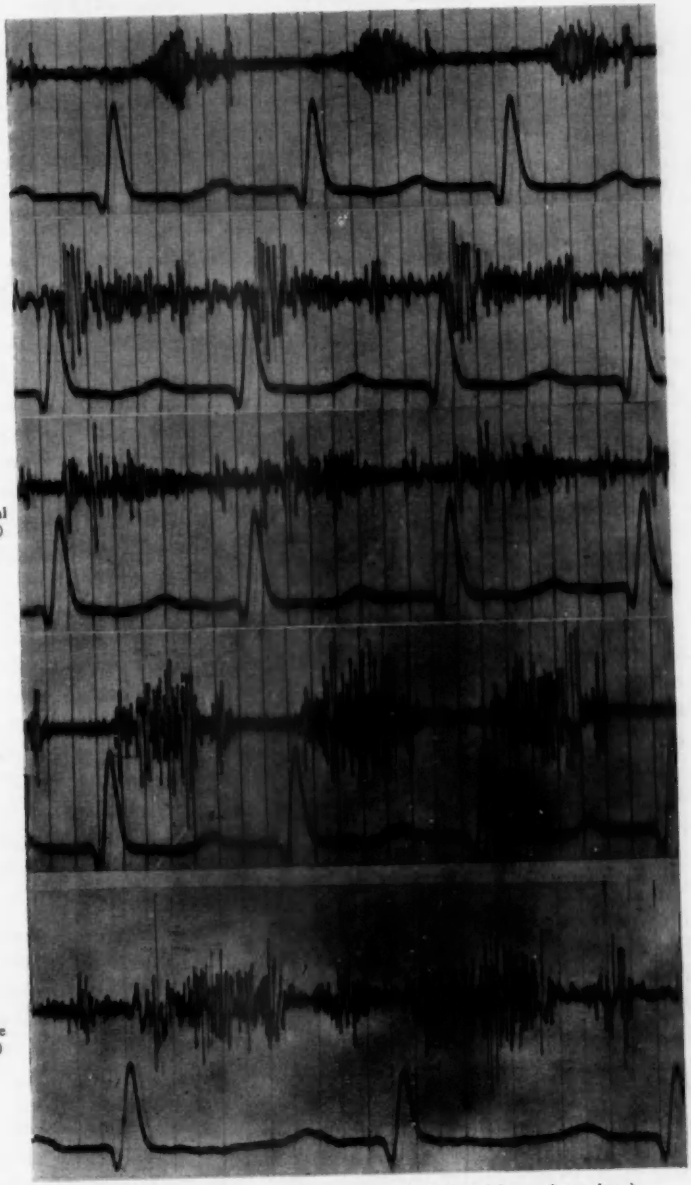

5 th i.c.s. left mid-axillary line (High)
Apex (5 th i.c.s.) (Medium)
3 rd i.c.s. left sternal border (Medium)
Pulmonary area (Medium High)
4 th i.c.s. left mammillary line (Medium High)

Fig. 4. Phonocardiograms taken on the time of admission (above 4 tracings) and on the time of transient recovery (lowest tracing). i) A systolic murmur with musical quality. The configuration varies from cycle to cycle. ii) Apical first heart sound shows no accentuation. The "Q–1" interval is within the normal limits (0.05″). Transmitted systolic murmur and short diastolic rumble with protodiastolic extra sound are seen. The interval between second heart sound and this extra sound is 0.08″. iii) Relatively loud ejection sound is seen. iv) The loud diamond-shaped systolic murmur at the pulmonary area. v) The diastolic rumble shows the crescendo-decrescendo configuration without presystolic accentuation.

operation. The operation* was performed successfully on May 16, but he expired 2 days after by congestive heart failure.

Findings at operation: A ring of greatly thickened and calcified pericardium was found around the middle of the pericardial sac. It passed across the base of the heart over the conus of the right ventricle and was attached laterally to the base of both atrial appendages. It then passed down into both atrio-ventricular grooves (Fig. 5). At the pulmonary ostium, it involved and compressed the ostium ex-

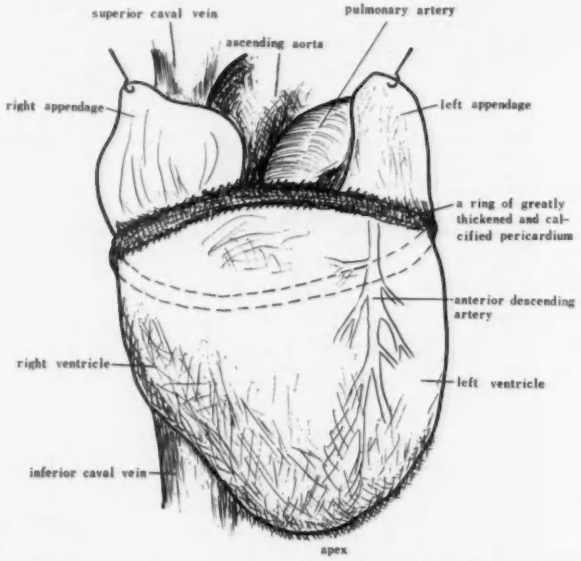


Fig. 5. Schematic sketch of the patho-anatomical features at operation. A hoop of calcified band compressed atrio-ventricular groove producing particulary pulmonary and mitral stenosis. Details seen in text.

ternally, but no organic stenosis of the pulmonary and the mitral orifices were noted. The free ventricular wall was slightly adhered with the parietal pericardium and the fibrous pleuropericardial adhesion was also noted. The diaphragmatic surface of the heart was firmly fixed by the fibrous adhesion without calcification.

Comment

According to Mounsey,[4] the areas of the exterior of the heart overlying the 4 valve rings are those where the greatest movement takes place, although these areas of the cardiac silhouette show least movement on screening of the heart. Hence, in the presence of the pericarditis, friction of the inflamed surface of the visceral and parietal pericardium is greatest here, thus giving

* This operation was performed by Prof. Seiji Kimoto, director of Department of Surgery, University of Tokyo. About two-thirds of the calcified ring was resected.

rise to a more intense inflammatory reaction. As the result, a dense thickening might be expected in these sites, and thus, the annular constriction might develop as an inevitable consequence. Gimlette[5] also noted that the pericardial calcification was usually present on the diaphragmatic surface and in the atrio-ventricular groove. Evans and Jackson[6] and Plum *et al.*[7] also mentioned that the calcified ring may occur in the atrio-ventricular groove in the cases with constrictive pericarditis.

As described by Paul *et al.*[8] and Eliasch *et al.*[9] the fibrous and calcifying process may penetrate into the left ventricle producing the functional mitral stenosis. However, the constriction of the great vessels is the rare instance.[10] In the series of Gimlette[5] and others,[6),11)-15] there was no such a case with constriction of great vessels. In our series including 19 cases during 9 years (1951–1960), such a case as in this report was not found, though a case with functional mitral stenosis was noted.

The clinical manifestation of the annular constrictive pericarditis is fundamentary the same with other types of constrictive pericarditis as stated by Mounsey.[4] However, in rare instance, the clinical picture, particularly the auscultatory finding, has the great difference as seen in our case.

Mounsey[4] reported a case with functional pulmonary, mitral and aortic stenosis which resulted from the external compression of the thickened inflamed pericardium. In our case a hoop of the annular pericardial band was calcified and the similar compression was present except the aortic ostium. This is responsible for the apical rumbling and pulmonary systolic murmurs. The absence of an accentuated 1st heart sound, mitral opening snap and the presystolic accentuation of the diastolic murmur, and the presence of the protodiastolic extra sound, although not typical in its figure, are incompatible with the pure mitral stenosis. The protodiastolic extra sound might result from the partial adhesions of the free ventricular wall, although it is caused by only the annular constriction.

A musical systolic murmur in our case heard at the beginning is also relatively rare auscultatory phenomenon in the cases of constrictive pericarditis. The cause of some musical murmurs remains unknown and it may be sometimes difficult to determine whether they are intracardiac or extracardiac in origin. In the cases of fibrous pericarditis, the friction rub is often heard, but it seldom has a musical quality. However, the disappearance of this musical murmur in our case was accompanied by the transient convalescence of the illness, and this fact may suggest that any exsudate was produced by the inflammatory process at first and was absorbed with the retirement of this incidence. This transient exsudation may cause development of the congestive heart failure in the cases of constrictive pericarditis, as stated by Murphy *et al.*,[16] though they did not described about the pericardial murmurs. But the relation of exsudation to the development of the congestive heart failure in our case was not confirmed since the time of occurrence of this murmur was obscure and it was not apparent whether the transient recovery from

the congestive heart failure was caused by absorption of exsudate or various therapeutic measures.

Summary

This report is an illustration of a case with calcified annular constrictive pericarditis showing the functional pulmonary and mitral stenosis. The brief comments were made upon the genesis of this entity and the unusual auscultatory findings.

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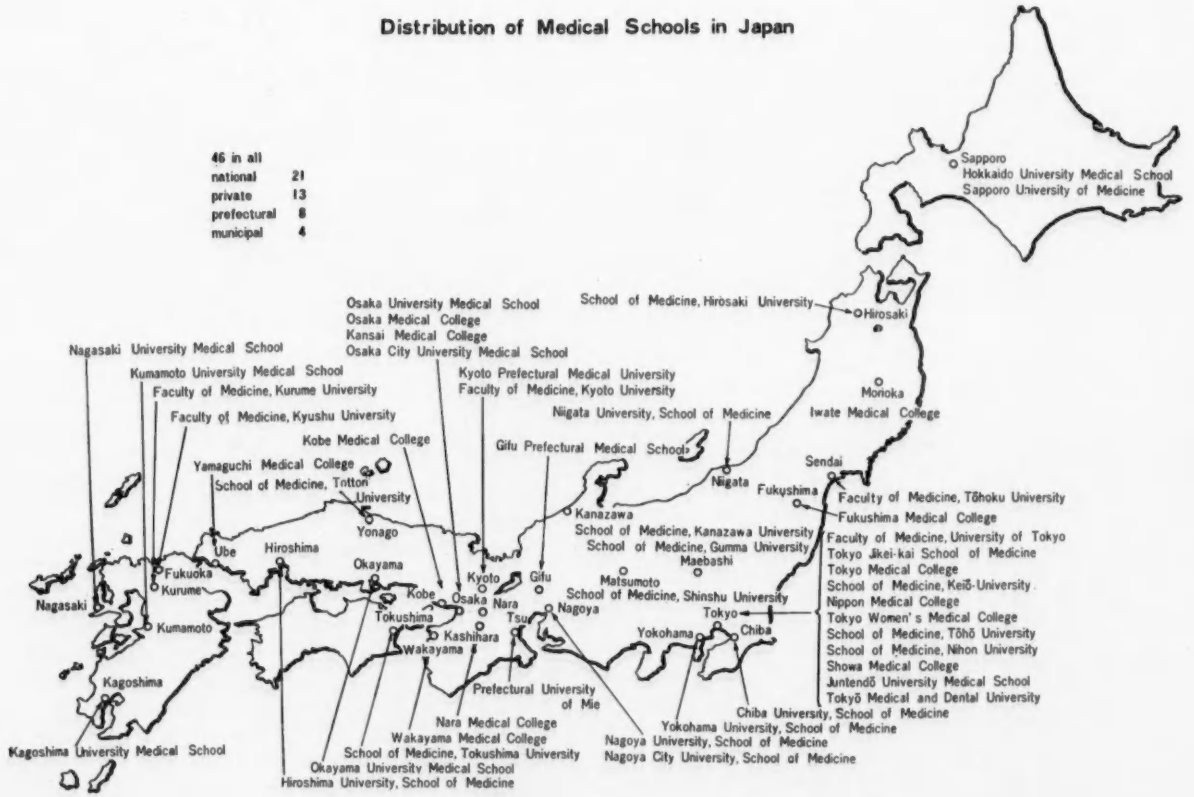

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